

# A TEXT-BOOK OF PATHOLOGY

*AN INTRODUCTION TO MEDICINE*

BY

WILLIAM BOYD

M.D., Dipl., Psych., M.R.C.P., Edin. F.R.C.P., Lond.,  
LL.D., Sask., M.D., Oslo, F.R.S.C.

*Fifth Edition,*

MOTILAL BANARSIDASS  
DELHI :: VARANASI :: PATNA

January, 1948

PRINTED IN INDIA BY SHANTILAL JAIN, SHRI JAINENDRA PRESS, BUNGALOW ROAD,  
JAWAHAR NAGAR, DELHI-7 AND PUBLISHED BY SUNDARLAL JAIN,  
MOTILAL BANARSIDASS, BUNGALOW ROAD, JAWAHAR NAGAR, DELHI-7.



## PREFACE TO THE FIFTH EDITION

In preparing a new edition of a scientific text-book an author must have before him the ideal expressed in the Scottish Psalter: "that to perfection's sacred height I nearer still may rise." No one realizes more fully than the author how far short of this ideal his best effort must inevitably be. So it is with the present effort. Much new material has been added, and some of the more glaring errors have been corrected. There are a number of new illustrations and one new color plate.

New sections have been added on the following subjects: stasis, lipotropic factors in relation to liver disease, the relation of vitamin C to wound repair, botryomycosis, Dubos' method of cultivating the tubercle bacillus, Tsutsugamushi fever, dermatofibroma, the carcinogenic action of acetyl acetaminofluorine, sclerosing hemangioma, liver lesions in pellagra, hypertensive heart disease, cardiac infarction without coronary occlusion, temporal arteritis, the mucosal respiratory syndrome, Löffler's pneumonia, giant-cell pneumonia, chronic disseminated tuberculosis, aspergillosis, intestinal lipodystrophy, alloxan diabetes, renal anoxia, malakoplakia of the bladder, interstitial-cell tumor of the testis, primary splenic neutropenia, splenic rupture in infectious mononucleosis, pyridoxin deficiency anemia, the anemia of infections, fibrous dysplasia of bone, hyperostosis frontalis interna, odontogenic tumors.

New material dealing with the following subjects has been included: cystic fibrosis of the pancreas, the pituitary-thyroid axis, the bone blood flow in Paget's disease, folic acid in relation to macrocytic anemia, the pathogenesis of poliomyelitis, hemochromatosis, burns, terminal endocarditis, Dock's observations on the structure of the coronary arteries, allergy in the production of lobar pneumonia, the mechanism by which pneumococci are destroyed, the apical localization of pulmonary tuberculosis.

The following sections have been rewritten: carcinogenesis in its relation to enzymes and viruses, silicosis and anthracosis, necrosis and cirrhosis of the liver, Cushing's syndrome, the Rh factor in congenital

when we discover that both the hemorrhage and the structural changes in the uterus have a common origin in disturbance of ovarian function the entire subject of the pathology of the endometrium acquires a different meaning. Unfortunately the physiological outlook is not always possible, and the pathologist may have to content himself with applying a great variety of names to an equally great number of states, the relationship and meaning of which he really does not understand. The student must learn to recognize that ignorance, however aptly veiled in an attractive terminology, still remains ignorance.

Physiology cannot be allowed to remain in its own watertight compartment. It must come out and contribute to the subject of pathological physiology. In the same way pathology must not confine itself to a study of states, but must include a consideration of disordered processes. As Sir Michael Foster once remarked with characteristic penetration: "The science of meteorology cannot be divided into the science of good weather and the science of bad weather." The study of morphology and pathological physiology, of altered structure and disordered function, must go hand in hand, greatly to the mutual benefit of both. A world of disordered function lies revealed in any lesion if we only have the eye to see it. A healed tuberculous scar in the lung should conjure up a sharp attack, a stubborn defense, temporary defeat, but ultimate victory.

It has become the fashion to regard morbid anatomy, both gross and microscopic, as somewhat of an outworn creed, a science as dead as the material with which it deals. But morbid anatomy is not dead and never has been, except in the hands of those whose dull minds would take the breath of life from the most vital subject. When taught by the masters of the past, morbid anatomy, so far from being dead, has been the living framework of a living body. The world of medicine did not think that there was anything dead about the "Cellular Pathologie" when Virchow poured the new wine of his vital spirit into the old bottles of tradition. And the bottles are not yet full.

There is much talk in the present day regarding the coördination of the various subjects of the medical curriculum. The study of pathology in the proper spirit is the best means of breaking down the partitions which separate the subjects, for such a study forms a common meeting-ground for anatomy, histology, physiology, biochemistry and clinical medicine. Pathology is not a pure science. The pathological changes are merely one side of a problem, of which the other side is furnished by the clinical picture. Each throws light upon the other

and neither is complete by itself. One of the most significant of the early symptoms of cancer of the stomach is anorexia, a distaste for food. A healthy appetite is dependent on the muscle tone of the stomach wall, and this tone is destroyed by the infiltration of carcinoma cells between the muscle fibers which forms so characteristic a feature of the microscopic picture. When this is realized, both the anorexia and the histological appearance will acquire a richer significance and a fuller meaning. To these statements an exception must be made in favor of general pathology, which may be studied in much the same way as a pure science is approached.

Pathology in relation to the living patient is the motif of this book. It is intended to serve as an introduction to medicine and surgery. The medical student who steps from the laboratory into the clinical years is apt to find himself in a very unfamiliar country where for a time he may be lost to a degree little guessed by his clinical teachers. In many schools the study of pathology is commenced at the same time as the study of medicine, surgery and gynecology. The student knows nothing about the symptoms caused by the pathological lesions he sees, so that he is unfitted to attempt that correlation of clinical symptoms with pathological lesions which forms one of the most valuable exercises in a course of morbid anatomy. With the idea of overcoming this difficulty the account of all the more important diseases is preceded by a brief summary of the clinical symptoms. Then comes the usual description of the morbid anatomy, and this is followed by an attempt to correlate the symptoms with the lesions. It is hardly necessary to defend the introduction of a brief account of symptoms, for the textbooks of medicine and surgery do not hesitate to preface the discussion of clinical manifestations by a survey of the morbid anatomy which frequently does not err on the side of brevity. For these reasons I have ventured to use the sub-title: "An Introduction to Medicine."

To the student the value of a persistent endeavor to correlate symptoms with lesions lies not so much in the number of facts which he may succeed in memorizing, as in the development of an attitude of mind which may color the whole of his future professional career. The clinical-pathological conference owes its popularity to the realization of this fact. Education can achieve no higher success than by leaving its abiding imprint on the mental outlook of those who come under its influence.

To the clinician who wishes to indulge in the periodic brain-dusting recommended by Osler there are few more valuable correctives than a renewed acquaintance with the facts of morbid anatomy as revealed

in the postmortem room. It is more than one hundred and thirty years since Bichat wrote the following words, but they are as true to-day as they were then: "You may take notes for twenty years from morning to night at the bedside of the sick upon the diseases of the heart, the lungs, the gastric viscera, etc., and all will be to you only a confusion of symptoms, which, not being united in one point, will necessarily present only a train of incoherent phenomena. Open a few bodies and this obscurity will soon disappear, which observation alone would never have been able to have dissipated. Dissect in anatomy, experiment in physiology, follow the disease and make the autopsy in medicine. This is the three-fold path without which there can be no anatomist, no physiologist, no physician."

WILLIAM BOYD

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# A Text-book of Pathology

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## PART I

### GENERAL PATHOLOGY

#### CHAPTER I

#### THE CONTENT OF PATHOLOGY

**PATHOLOGY** is the study of the basis of disordered function. More fully stated, it may be considered to be the study of the processes and causes of disease and of its nature. It is concerned with answering the questions how and why in relation to disease. At first sight there would appear to be no difficulty in forming a conception of what we mean by disease, but the more closely the matter is considered the more difficult does it become. Health is a condition in which the organism is in complete adaptation to its surroundings. Disease is a change in that condition as a result of which the organism suffers from discomfort (dis-ease). But the question of health or disease may be considered from the point of view of the physician or of the pathologist, and the result will be correspondingly different. A man may die from the terrible convulsions of strychnine poisoning, yet the pathologist will find no structural change or *lesion* to which he can point as the cause of death. On the other hand a person in perfect health may be found at autopsy to have a tuberculous lesion of the lung or chronic disease of the heart valves which has been compensated for by cardiac hypertrophy. Are we to consider such a person in a state of health or of disease? It has been said that "health is harmony, disease discord," and Adami remarks that the harmony may be in a minor key. So long as there is harmony, even though the price of that harmony be the structural alterations of compensation and resistance, the person is in a state of health to the clinician, but to the pathologist the lesions in the organs have to be interpreted as evidence of disease.

Clinical medicine is concerned with disturbances of function as manifested by the symptoms of the patient, while pathological anatomy is concerned with changes in structure. But it is essential that the two go hand in hand, for both present only one side of the picture. The pathologist performing an autopsy on a case of typhoid fever for the first time could no more deduce the clinical symptoms from the

lesions which he finds after death than could the clinician forecast the structural changes from a study of the living typhoid patient if he had never attended an autopsy. The pathologist who never goes on the wards is comparable to the clinician who never enters the autopsy room.

Pathology, then, in the sense of morbid anatomy and morbid histology, is the study of the tissue alterations which develop as the result of pathogenic or disease-producing agencies. It is true that in actual practice these alterations may be of so fine a character as to escape detection, but this is merely because the methods at our disposal are still comparatively crude. This is even more true of the so-called functional disorders which form so large a part of the physician's practice. In spite of these limitations it can still be said that pathology is the substructure of diagnosis, for, as Hamman points out, diagnosis is concerned more with structural change than with functional disturbance.

It is easy to make the fatal mistake of regarding pathology as being concerned merely with states, particularly the state at the moment of death. But disease is not a state; it is rather a *process* ever changing in its manifestations, a process which may end in recovery or in death, which may be acute and fulminating in its manifestations, or which may represent the slow ageing of the tissues brought about by the sharp tooth of time. To rest content with recognizing and correctly naming a mitral stenosis at autopsy is to be satisfied with playing the part of a technician. For the lesion has been present during many years of life, and its presence is not sufficient to explain the final end. Moreover the pathologist has to try to explain not only why the patient died but how he was able to live. As Boycott remarks: "I do not wonder that people die; that is easy enough. What I marvel at is that they go on living with bodies so maimed, disordered, and worn out." We must concern ourselves with processes which have got out of place, out of time, and out of tune, as well as with disorder of structure, for disease may be defined as merely a summation of chemical reactions that have gone wrong. It is the high function of the pathologist not merely to attach correct labels to the lesions when he sees them, but to reconstruct the course of events from the earliest inception of the disease to the final moment when we have to fall out of "the splendid procession of life." In speaking of the microscopic study of the kidney from a case of chronic Bright's disease, Rich paints a picture of the true pathologist: "In that minute film of tissue he plainly sees dynamic disturbances of renal function with alterations in the composition of the blood, the tissue fluids, and the urine, the elevated blood-pressure, the hypertrophied heart with its constant threat of decompensation, the anemia with its debilitating effects, the disturbances of vision, the impending symptoms of uremia. In brief, in that bit of dead tissue, altered by the effects of fixatives and stains, he sees the general outlines of a living patient progressing along the path from health to death."

But the lesions and the functional disorders to which they give rise are not everything. There are the hidden qualities of tissue and blood to be considered, those qualities which determine the result, favorable or otherwise, of the interaction between the patient and noxious influences. The more searching the inquiry, the more difficult becomes the separation of the concepts of health and disease, till finally there is danger of arriving at the conclusion that all things medical belong to the pathologist.

It must be borne in mind that it is the whole patient who comes to the doctor's office, not just a disordered liver, a cardiac lesion, or a septic throat. In the words of the old French proverb: "There are no diseases, but only sick people." It has been estimated that at least 50 per cent of all patients consulting a physician have no real organic trouble. From this it is evident that what is usually called morbid anatomy constitutes only one part of the general subject of pathology. It is the part, however, with which this book is primarily concerned.

The structural changes observed at autopsy are not due to death, for if death be sufficiently sudden, as from poisoning by prussic acid, no change of any kind may be detected. They are the result of the processes of degeneration, reaction, repair, and growth disturbance which have preceded death. Pathology is therefore concerned with a study of these processes and with their causes. They may be grouped under a comparatively few headings, and a study of these general processes comprises the subject of General Pathology which forms the first part of this book. After completion of this study it is possible to turn to the various organs and systems and apply the general principles to specific instances. The study of heart disease, kidney disease, nervous disease, etc., comprises the subject of Special Pathology.

The *causes of disease* are known as the *etiological* factors. The *method* by which the lesions are produced by these factors is known as *pathogenesis*. Etiology tells us *what* sets a process in motion, pathogenesis *how* it is set in motion. Nothing would be gained by discussing etiological factors in detail at this point, as the student is unfamiliar with the diseases which they produce. Suffice it to say that they may be gathered into seven main groups. These are: (1) congenital or hereditary tendencies or defects, with which may be included the difficult subject of constitution; (2) insufficiency of food and oxygen, including those conditions known as deficiency diseases; (3) infections by the various pathogenic microorganisms; (4) animal parasites; (5) trauma; (6) physical irritants; and (7) chemical poisons. Reference to the table of contents will serve to amplify this brief summary of the processes and causes of disease dealt with in the subject of General Pathology.

#### ADDITIONAL READING

ADAMI: Principles of Pathology. Philadelphia, 1910, p. 21.

BOYCOTT: Lancet, 1933, 2, 846.

HAMMAN AND RICH: Clinical Pathologic Conference, Internat. Clinics, 1933, 1, 198.

## CHAPTER II

### DEGENERATIVE PROCESSES AND DISTURBANCES OF METABOLISM

THE group of processes known to pathologists as the degenerations forms rather a heterogeneous collection. They can be studied from the point of view of the abnormal materials which appear in the cells or the intercellular substance. It is better to take a wider view and regard them as indications of sickness on the part of the cells, as disorders of metabolism which suggest what Galton has called the steady and pitiless march of the hidden weaknesses in our constitution. They are the fingerprints of disease left on the tissues. Some are slight and transitory; others proceed to a fatal termination.

#### CLOUDY SWELLING

The condition known from its gross appearance as cloudy swelling, also called *albuminous degeneration*, is much the commonest of the degenerations. It is an indication of a disturbance of cell metabolism which may occur as the result of any toxemia. The toxin may be the product of any infection or infectious fever such as pneumonia or septicemia; it may be an inorganic poison such as corrosive sublimate, or it may be a toxin of endogenous origin in such conditions as jaundice and diabetes. From this it will be seen how extremely common the condition of cloudy swelling must be. Moreover postmortem autolysis produces an identical picture, so that if more than a few hours have elapsed between death and the autopsy, cloudy swelling of some degree will be found no matter from what disease the patient may have suffered.

The principal organs showing cloudy swelling are the kidney, the liver, and the heart muscle. The organ affected is slightly enlarged, owing to swelling of the cells of which it is composed. It is pale, the bloodvessels being compressed by the swollen cells. The cut surface has a rather cloudy appearance, slightly opaque, as if scalded in hot water.

The *microscopic appearance* can best be studied in the highly specialized cells of the convoluted tubule of the kidney. (Fig. 1.) The cell presents two abnormal features: (1) it is unduly granular, and (2) it is swollen so that it projects unevenly into the lumen of the tubule. The distinction between the degenerated convoluted tubules with highly irregular outline and the apparently unaffected collecting tubules is often very striking. As the condition advances the cell may break down and the granular material is discharged into the lumen of the tubule. Fatty globules may appear in the cytoplasm, an association of fatty degeneration with cloudy swelling. The granules are albuminous in character, and can be distinguished from fatty granules

by the fact that they are soluble in acetic acid and insoluble in lipoid solvents such as chloroform, but as the condition advances true fatty droplets resembling myelin may appear. Part at least of the granular appearance seems to be due to changes in the mitochondrial rods, which break up into granules that fuse to form larger masses. The swelling of the cell is due to edema.

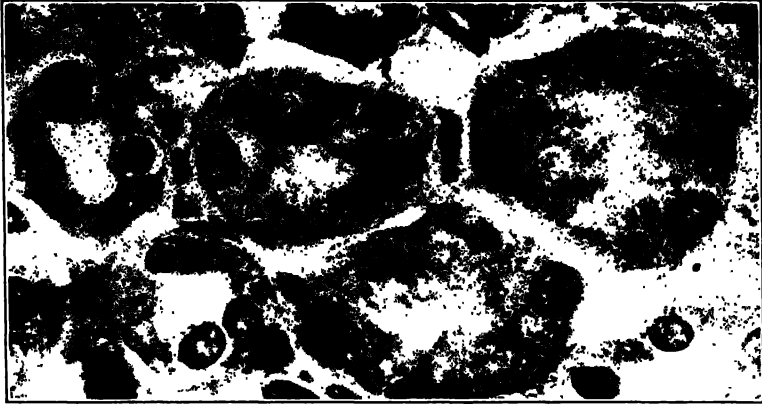


Fig. 1.—Cloudy swelling of kidney. The cells of the convoluted tubules show marked swelling and granularity, while those of the collecting tubules (at the left) are but little affected.  $\times 1000$ .

Cloudy swelling closely resembles the early stages of postmortem autolysis. In both there is granularity and swelling of the cytoplasm. It can be shown that organs the seat of cloudy swelling undergo very rapid postmortem autolytic changes. The interest of cloudy swelling lies in the fact that it is an indication that the patient has suffered from a toxemia, exogenous or endogenous. Its significance is largely discounted because of two reasons: (1) the multiplicity of the conditions, including terminal infections, which may cause it; (2) its occurrence as a postmortem phenomenon unless the material is very fresh.

**Hydropic Degeneration.**—In this condition, also called serous degeneration, epithelial cells become distended with clear fluid, sometimes to such an extent that they actually burst. The change is best seen in acute inflammation of surface epithelium, as in blisters, smallpox, and anthrax. The osmotic pressure of the cytoplasm is altered, so that the cells take up fluid from the surrounding tissue. Detached cells lying in watery fluid undergo a similar change. The cells of a carcinoma, especially carcinoma of the cervix, may show marked hydropic degeneration.

## FATTY DEGENERATION

Fatty degeneration is a condition in which degeneration of the cell is accompanied by the appearance of fat droplets in the cytoplasm. As we proceed we shall find that this definition says too much and at the same time too little. The presence of visible fat in cells where it

normally cannot be seen is of twofold interest: (1) It is a sure indication that the cell is sick (except in the case of the liver), and (2) the fat itself is a substance singularly interesting to study and easy to demonstrate. No intelligent discussion of the behavior of fats in disease is possible without some understanding of what is going on under conditions of health.

**Distribution and Transport of Fats.**—Fat is present in the body in two very different forms: (1) as depot fat, and (2) as tissue fat. The depot fat is visible fat giving the usual chemical reactions, and collected chiefly in the subcutaneous tissue and the omentum, where it is known as adipose tissue. The fat cell of adipose tissue is a connective-tissue cell distended with neutral fat which displaces the nucleus to the side of the cell. In manutrition the fat cells are much smaller than when a person is well nourished. As the result of insulin and glucose therapy the diameter of the fat cells may be doubled; before treatment they may be small and thick-walled, while after treatment they become distended and thin-walled. In the fetus the fat cell at first has a central nucleus and granular cytoplasm. Fine globules of fat appear in the cytoplasm around the granules, enlarge, and coalesce so as to form one large globule which occupies the entire cell. In areas where adipose tissue has been destroyed the new cells are sometimes of the fetal type at first. The tissue fat exists in a combined or invisible form so united with the protoplasm of the cells that it cannot be demonstrated by histological methods unless it becomes visible as the result of pathological change. For long the question was asked: Where does this tissue fat come from? It used to be thought that the cell proteins could become changed into fat. It now appears likely that there are two great sources of fat: (1) the fat in the food and that in the fat depots, and (2) the carbohydrates. With the latter we are not concerned here. As fats are insoluble it is evident that the fat in the food and the depots must undergo some change before it can be carried by the blood to the cells. A brief review of some chemical facts therefore becomes necessary.

The fats may be divided into two great groups: (1) neutral fats, and (2) lipoids. Together they form the *lipins*. The *neutral fats* are esters of the triatomic alcohol glycerin and a fatty acid. The three chief fatty acids are palmitic, stearic, and oleic. The neutral fats of the food are broken up by digestive ferments into their primary constituents, glycerin and a fatty acid. The fatty acid combines with an alkali to form a soap, and as this is soluble it can be absorbed and carried to the cells, where the fatty acid is liberated from the soap, and recombined with glycerin to form neutral fat. The classical experiments of Rosenfeld prove conclusively that the depot fat is derived mainly from the fat in the food. A dog was fed on mutton fat, which has a higher melting-point than its own fat so that it can be easily recognized. In time the fat in the depots came to consist entirely of mutton fat, so that the animal was in truth a dog in sheep's clothing. Depot fat may also be formed from the carbohydrates of the food. This change does not take place readily in man, but with great ease in swine and geese, so that these animals can be fattened on a purely carbohydrate diet. Proteins take no part in fat formation.

In the fat in the depots the *fatty acids* are in a saturated form and are therefore inactive and cannot be utilized directly. In the tissues the fatty acids are unsaturated so that they are available for active metabolism. It seems probable that the liver acts as an intermediary station, desaturating the fats whether of the food or of the depots so that they can be readily utilized. The iodine value which indicates the degree of saturation is low in depot fat, high in the tissues, and intermediate in the liver. We shall find, as is but natural, that in respect to fatty degeneration and infiltration the liver must be separated from all the other organs.

The *lipoids*, which resemble fats in being soluble in fat solvents such as

alcohol, chloroform, and ether, are even more essential to the life of the cell than the fats themselves. The chief of the lipoids are cholesterol and the phospholipins or phosphatides. *Cholesterol* or its ester is present in the cytoplasm of all cells. It forms a most important constituent of bile, from which it was first isolated and derived its name (*chole*, bile; *stereos*, solid), of the envelope of red blood corpuscles, and of the adrenal cortex. In pregnancy there is a great increase in the cholesterol of the blood, and it is present in large amount in the corpus luteum of the ovary. At the end of pregnancy there is an outpouring of cholesterol in the milk, and the blood cholesterol returns to normal. The medullary sheath of the nerves and the white matter of the brain and spinal cord is composed of *myelin*, which is made up of several lipoids, the chief being cholesterol. Like cholesterol, myelin is anisotropic, i. e., doubly refractile to polarized light. *Lecithin*, a phospholipin or combination of neutral fat with phosphoric acid and a nitrogenous base, is another important lipid constituent of cells. It enters into the formation of myelin. Cephalin is a phospholipin found principally in the central nervous system.

**Staining Methods.**—The various methods for the demonstration of lipins (neutral fat and lipoids) are of particular importance, and must be thoroughly understood by the student of fatty degeneration. In the first place it is evident that the ordinary methods of paraffin and celloidin embedding are not permissible, for they entail the use of such fat solvents as chloroform, xylol, and ether. Frozen sections are therefore used for this work. By some methods to be considered presently it is possible to convert the fat into an insoluble form, after which paraffin or celloidin embedding may be used.

The simplest staining method is the use of the azo series of *aniline dyes*, Sudan III or Scharlach R (scarlet red), on frozen sections which may be fresh or fixed in formalin. The Sudan gives an orange color, the scarlet red a brilliant red. There is no chemical union between the fat and the dye; the latter is more soluble in fat than in alcohol, so that it leaves the alcoholic solution and becomes dissolved in the fat. Cholesterol and its ester stain less brilliantly than neutral fats with scarlet red. These dyes do not stain normal myelin nor the fatty acids, but when the myelin is broken down it is readily stained. A fatty acid can be stained by any *basic aniline dye* such as methylene blue or methyl violet. The fat is first hydrolyzed into a fatty acid and glycerin by the action of dilute acid or even by exposing the section to the CO<sub>2</sub> of the air. The *oxazine dyes*, of which Nile blue sulphate is the chief one used, act as double stains. One stain is an oxazine base and stains fatty acids blue in the usual way. The other stain is formed by decomposition of the oxazine base in watery solution with the formation of a bright red dye which is soluble in neutral fat though chemically indifferent to fatty acids. By this method of Lorrain Smith the constituents in a mixture of neutral fat and fatty acids can be stained separately.

The use of *osmic acid* is the oldest method of staining fat and it is still one of the most useful, particularly for recent degenerations of the nervous system. The substance is really a peroxide of osmium which is reduced by the fat, and forms a black compound with it which is insoluble in xylol. Thus osmic acid is a fixative as well as a stain, and tissue thus fixed can be embedded in paraffin and cut without losing its fat. Osmic acid stains neutral fat and lipoids such as cholesterol ester and myelin, but the tissues must not be kept too long in formalin, else they will become oxidized.

*Marchi's method* is an offshoot of the osmic acid method and depends on the principle of selective oxidation. When a tissue is kept for a certain period in a solution of potassium bichromate the easily oxidized fats become oxidized. Osmic acid is then used; this stains any unoxidized fats but not those already oxidized. The method is of supreme value in examining recent degenerations and injuries of the nervous system not more than a few weeks old. Normal myelin is readily oxidized and so fails to stain, but the myelin of degenerating medullary sheaths is oxidized very slowly by the potassium bichromate and is readily stained by the osmic acid. In time the myelin disappears and then,

of course, the method is inapplicable. In a recent injury to the internal capsule (hemorrhage, etc.) the degenerated fibers can be traced down the pyramidal tract in the cord with the greatest exactness by means of Marchi's method. This has been a potent weapon in the hands of the physiologist who can produce his own experimental lesions in the brain, and then follow the course of the degenerating nerve fibers. From what has been said it is evident that normal myelin is stained by osmic acid but not by Marchi's method.

*Weigert's method* for staining myelin may be looked on as the converse of the Marchi method, for by it only the normal myelin is stained. It is used for old degenerations in which the degenerated myelin has disappeared. When fat is only partially oxidized by potassium bichromate and thus still unsaturated it has the power of combining with hematoxylin to form an insoluble dark blue lake. As the stained fat is now insoluble the tissue can be embedded in paraffin or celloidin. The method is principally used for demonstrating old degenerations of the nervous system, the myelin of the normal fibers staining dark blue and the degenerated fibers remaining unstained.

Another method of great value in differentiating lipoids from neutral fats is *examination by polarized light*. When Nicol's prisms are placed on the microscope and a frozen section is then examined, cholesterol and cholesterol ester which are anisotropic, *i. e.*, doubly refractile, appear as brilliant bodies against a black background, the ester often taking the form of a Maltese cross of light. Neutral fats are not anisotropic, and therefore remain invisible. This method is sometimes very useful in pathological conditions.

**The Nature of Fatty Metamorphosis.**—From the days of Virchow a distinction has been drawn between two forms of fatty change: (1) fatty degeneration, and (2) fatty infiltration. These may both be included under the term fatty metamorphosis. In fatty degeneration according to Virchow, owing to disease of the cell the proteins of the cytoplasm were converted into fat, whereas in fatty infiltration too much fat was carried to an otherwise healthy cell and appeared there in visible form. In degeneration the fat droplets were small and numerous, whereas in infiltration they fused together to form a few large drops. The foundation on which this hypothesis was based is ~~largely invalidated by the knowledge that fats are not formed from proteins.~~ Dible, who has studied the matter very thoroughly, believes that fatty change in the liver is entirely due to transfer of fat from fat depots, and is therefore in the nature of an infiltration. In experimental starvation the liver quickly becomes fatty, the degree of the change depending on the amount of available fat in the body. When an animal is starved until the fat in the depots is exhausted, poisoning with phosphorus fails to produce fatty degeneration of the liver. It seems probable that the factor of starvation plays a part in the genesis of many cases of fatty liver owing to interference with metabolism there. In other organs, *e. g.*, heart muscle and kidneys, a similar mechanism seems to be responsible for the fatty change. The old idea of *fat phanerosis* (*phaneros*, visible), an unmasking of the invisible fat already present in the cytoplasm of these organs, must now be replaced by the concept of fatty infiltration (Popjak). The experimental work of Dible and Govan shows that "fatty degeneration" of the heart and kidney may be produced by the intensive administration of fat in the diet. In such cases the fatty metamorphosis appears to be an infil-



tration rather than a degeneration. There is still another form of fatty metamorphosis which may be called lipoidal degeneration, characterized by an increase in the amount of visible lipid. This may be due to a true infiltration or to a setting-free of previously combined lipid. It is seen in the kidney, adrenal, ovary, gall-bladder, and some tumors, and will be discussed in a later paragraph.

**Causes.**—There are two great *causes of fatty metamorphosis*: (1) the action of toxins, and (2) lack of oxygen. It is possible that the first factor acts by virtue of interfering with the proper oxygenation of the cell, which would make this the basis of all fatty degeneration. The poisons may be divided into organic and inorganic. The organic poisons are bacterial toxins, by far the most important etiological factor. Any of the acute infections or such a chronic infection as tuberculosis may act in this way. Of the inorganic poisons phosphorus, chloroform, and alcohol are the most important. Phosphorus poisoning is seldom seen nowadays. If a person dies some days after prolonged chloroform anesthesia, marked fatty degeneration particularly of the liver will be found. These metabolic disturbances are the basis of the so-called delayed chloroform poisoning. Chronic alcoholics, especially heavy beer-drinkers, may show marked fatty degeneration of the liver. Insufficient oxygenation as a cause is seen in severe anemias both primary (pernicious) and secondary. The degeneration which is well seen in the heart and kidney as well as the liver is most marked in pernicious anemia. Loss of the local blood supply may lead to fatty degeneration. In the atrophy of old age, disuse, and chronic venous congestion the cells often show fatty degeneration, probably caused by insufficient oxygenation. Softening of the brain due to ischemia is characterized by marked fatty metamorphosis, the myelin breaking up into droplets which are readily stained with Sudan. Fatty degeneration can be studied experimentally in tissue cultures. Many of the cells in such a culture contain minute droplets which can be stained with Sudan. If the metabolism of the cells is interfered with by the addition of alcohol or phosphorus, the fat droplets become much larger and more numerous.

The *causes of lipomatosis* or adiposity are: (1) excessive ingestion of fats and to a lesser degree of carbohydrates, and (2) factors which interfere with the proper utilization of fat. Among the latter are lack of exercise, advancing years, sex (female), race (Hebrew), and sometimes dysfunction of one of the ductless glands, particularly the pituitary as in the disease known as dystrophia adiposo-genitalis.

**Fatty Degeneration in Special Organs.**—Although fatty degeneration may affect the cells of any organ, it is most readily observed in the liver, the kidney, and the heart.

The *liver* is paler and yellower than normal, soft in consistence, the edges are swollen and rounded, and the cut surface may be slightly greasy. The organ may be considerably enlarged, as in the beer-drinker's liver. Microscopically the liver cells are filled with fat drop-

lets which can be readily stained with Sudan, osmic acid, and the other methods already described. (Figs. 2 and 3.) All of the fat is neutral fat. In the past there has been much discussion as to whether a given liver shows fatty degeneration or fatty infiltration, but with our present knowledge that all the fat comes from the fat depots, the matter may well be dropped. Marked fatty changes in the liver are seen in severe anemia, pulmonary tuberculosis, diabetes, and chronic venous congestion of the liver, conditions in which oxidation of the fats is interfered with. The liver plays an important part in the oxidation of fats and the formation of ketone bodies. The multiplicity of conditions which will cause fatty metamorphosis in the liver suggests



FIG. 2.—Fatty liver. The liver cells are occupied by large clear droplets of fat.  $\times 375$ .



FIG. 3.—Fatty liver stained with osmic acid. The fat is at the periphery of the lobules.  $\times 75$ .

that one of the most easily disturbed properties of the liver cell is its ability to deal with fat. The less the oxidation, the greater is the accumulation of fat. If an animal is first starved it is impossible to produce fatty changes in the liver by the ordinary experimental methods, as no fat is transported from the depleted depots.

In recent years much interest has been aroused by the so-called *lipotropic factors*, a term suggested by Best to indicate substances which prevent or remove the accumulation of excess fat in the liver. Under normal conditions the amount of fat in the liver is fairly constant. An accumulation of fat indicates a change in metabolism. This may be due to failure in the transport of fat from the liver or to

too rapid withdrawal from the fat depots for the liver to deal with. Phospholipids are essential for the transport of fat, and as choline promotes the formation of phospholipids absence of this food factor from the diet leads to the rapid accumulation of enormous amounts of fat in the liver. This is true also of choline precursors such as methionine. The effect of protein on fat transport seems to be due to the transfer of methyl groups from methionine for the synthesis of choline. Pregnancy damages the liver because the lipotropic factors are side-tracked to the fetus. Dietary casein has a lipotropic effect; it is possible that this may be due to its methionine content. Thiamin appears to have an antagonistic action on the lipotropic effect of choline. It is of interest to note that attention was first drawn to the possibility of lipotropic factors by the accumulation of large amounts of fat in the livers of depancreatized dogs maintained on insulin but an inadequate diet. Another lipotropic factor named lipocaic has been extracted from the pancreas.

Accumulation of fat in the liver can be produced experimentally in a variety of ways: (1) by the absence of such lipotropic factors as choline, methionine, betaine, and inositol; (2) by pancreatectomy; (3) by the administration of toxic substances such as chloroform; (4) by a high fat-low protein (casein) diet; (5) by anterior pituitary extract (ketogenic fraction). All fatty livers are not alike, and the effect of lipotropic factors depends on the character of the lipids. Thus choline does not prevent fat accumulation due to anterior pituitary extract but lipocaic does, nor does choline have much effect on the fatty livers due to toxins and starvation. For further information on these matters the reader is referred to the reviews by Best and by McHenry and Patterson.

Fatty infiltration of the liver caused by a high fat-low protein (casein) diet tends to lead to cirrhosis (fibrosis). This may be associated with necrosis of the liver cells or may be independent of it. There is apparently direct stimulation of the fibroblasts with resulting cirrhosis.

The *kidney* is pale, but is not necessarily enlarged. The cells lining the convoluted tubules contain large numbers of small fat droplets. This fat is chiefly lipid in the moderate grades of degeneration, although neutral fats appear in the more severe forms. The droplets first appear between the nucleus and the base of the cell, but presently they may fill the entire cell. As the condition is a true degeneration the nucleus and cell structure may show degenerative changes in the advanced stages. If the collecting tubules show any fatty change it is only slight in degree.

In the *heart* fatty degeneration is especially marked in pernicious anemia and other severe forms of anemia. The heart is soft and flabby so that in extreme cases it may collapse in mushroom fashion when held up by the apex. The change is best seen in the papillary muscles of the left ventricle, where it produces a speckled appearance of the muscle under the endocardium, to which the names of "thrush breast"

and "tabby cat" have been applied. Other parts of the wall of the ventricles may also show marked mottling. Under the microscope the change is seen to be due to a replacement of the muscle fibers (which are really cells) by numerous droplets of fat often arranged in longitudinal rows. (Plate I and Fig. 4.) Normal heart muscle contains no visible fat, and yet it yields 15 per cent of fat when extracted with ether. A heart the seat of marked fatty degeneration is full of visible fat, yet extraction with ether may show only a very slight increase.

In a *medullated nerve* the fatty metamorphosis known as *Wallerian degeneration* may occur as the result of injury to the nerve fiber either in a peripheral nerve or in the central nervous system. The myelin becomes broken up into droplets which can be beautifully demonstrated by means of Marchi's method. This change will be described in detail in the section on the Nervous System.

*Lipomatosis* is a local adiposity of the connective tissue due to fatty infiltration. It is best seen in the heart, where large droplets of fat lie in the connective tissue between the muscle bundles, and may interfere considerably with the action of the organ. If the extra supply of fat is cut off the lipomatosis will disappear.

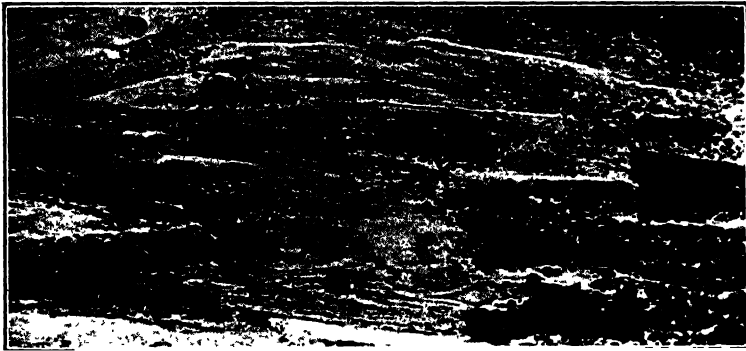


FIG. 4.—Fatty degeneration of heart. Frozen section stained with Scharlach R showing droplets of fat.  $\times 450$ .

**Lipoidal Degeneration.**—In ordinary fatty degeneration and infiltration the fats concerned are neutral fats. There is in addition an important group of pathological changes involving the lipoids, mainly cholesterol and cholesterol ester. These lipoidal changes may be both in the nature of degeneration and infiltration. Cholesterol, which is not a true fat but an alcohol, is normally present in large amount in the adrenal cortex, which appears to remove it from the blood and store it. In addition it can be demonstrated in the interstitial cells of the testis and ovary. It is a constituent of all the cells of the body, but in an invisible form. When the cell undergoes autolysis the cholesterol is not destroyed, so that it may become visible either as a needle-shaped crystal or as a flat plate with one corner bitten out.

## PLATE I



### Fatty Degeneration of Heart

The majority of the muscle cells are loaded with fat stained red with Scharlach R.



The nature of these crystals as well as that of the ester can be beautifully demonstrated by examining frozen sections under crossed Nicol's prisms; the brilliantly white anisotropic material stands out against the black background. Cholesterol crystals may be found in caseous tissue, infarcts, old hemorrhages, atheroma, degenerating goiters, dermoid cysts, hydrocele fluid, etc. The yellow patches on the inner surface of the aorta in atheroma consist mainly of lipoids, but neutral fats are also present. The characteristic spindle-shaped clefts in the tissue are often associated with giant cells, indicating a foreign body giant cell reaction. This reaction is best seen in the tumor-like masses called xanthomas. The cholesteatomatous masses which occasionally occur in the ear and the cranial cavity consist largely of cholesterol. Two conditions which more closely resemble true fatty degeneration than those already mentioned are cholesterolosis of the gall-bladder (strawberry gall-bladder) and those forms of Bright's disease which are associated with marked albuminuria and edema, *i. e.*, nephrosis and wet nephritis. In these conditions there is a remarkable collection of cholesterol in the epithelial cells of the gall-bladder and kidney respectively, which will be considered in detail when these diseases are described. When cholesterol ester is set free as the result of lipoidal degeneration it is often taken up by phagocytic cells, giving the cytoplasm of these cells a vacuolated appearance. These *foam cells* are seen to best advantage around an area of brain softening, but they are found in degenerating goiter and many other situations.

*Lipoid storage* is a condition in which large quantities of lipoid accumulate in certain cells of the body. When an animal is fed on a diet rich in cholesterol, the lipoid stored in the body is increased in amount, and if enough is used an atheromatous-like degeneration of the aorta may be produced. As a result of disease there may be very marked lipoid storage, especially on the part of the cells of the reticulo-endothelial system. In occasional cases of severe diabetes and even more rarely in obstructive jaundice this system of cells becomes loaded with lipoid, so that the organs involved (spleen, liver, etc.) become enlarged. Even more striking examples of lipoid storage are afforded by Gaucher's disease and Niemann's disease, obscure conditions of disturbed lipoid metabolism associated with enormous enlargement of the spleen owing to the extreme distention of all the reticulo-endothelial cells with lipoid. Christian's syndrome seems to be another example of the same condition.

Tissue reactions to lipids, a term which signifies a heterogeneous group that includes fats, oils, waxes, phospholipids and sterols, are varied. These reactions occur when the fats are not completely metabolized. The reaction about unhydrolyzed fat is similar to that against an inert oil-like liquid petrolatum. With hydrolysis of the fat and liberation of fatty acids there may be acute necrosis or a non-specific reaction on the part of fibroblasts and macrophages. Insoluble soaps excite a foreign body giant-cell reaction. The various reactions have been fully discussed by Hirsch.

**Lipemia.**—A marked increase in the lipoids of the blood is known as lipemia. The normal fat content of the blood is 0.6 to 0.8 per cent. This consists for the most part of lipoids with very little neutral fat. In lipemias the chief increase is usually in the cholesterol, with some increase of lecithin and fatty acids. Such a condition is called *hypercholesterolemia*. There is often a marked increase of the lipoids in diabetes, chronic alcoholism, nephrosis, the wet stage of nephritis, and obstructive jaundice. In pregnancy there is a slight increase and in eclampsia a marked increase. In diabetic coma there may be as much as 20 per cent blood fat. In the more marked cases the blood serum has a milky appearance, so that the more severe grades can readily be recognized with the naked eye. Deposits of the lipoids may occur in the skin in diabetes and in obstructive jaundice, giving rise to little flat plaques of a yellow color, a condition known as *xanthoma*.

**Progressive Lipodystrophy.**—This strange disturbance of fat metabolism is characterized by a symmetrical and progressive loss of subcutaneous fat in the face, arms and upper part of the body, associated with undue deposition of fat in the buttocks and lower limbs, occurring in children, usually girls. In extreme cases the skin rides loosely over the muscles, giving the patient a cadaver-like expression. To the eyes of one observer the lower half of the body looked like a model of one of Rubens' paintings, while the upper half resembled one of the witches in Macbeth. The adipose tissue of the affected parts is unable to store fat, no matter how much the patient may eat. The cause is unknown.

**Insulin Lipodystrophy.**—A local atrophy of subcutaneous fat may follow the prolonged use of insulin if it is injected continually in the same area. This may be due to a lipase in the insulin or to damage to the fat envelopes. There may be a local infiltration of lymphocytes and plasma cells.

### GLYCOGEN INFILTRATION

Glycogen is the storage form of carbohydrates, and corresponds to the starch of plants. It occurs in the body in a labile and a stable form. Th-labile form, which represents by far the greatest amount, is present in abundance in the liver (38 per cent of the total amount in the body) and in the muscles (44 per cent). It is converted into glucose with great ease, and rapidly disappears from the tissues after death. As it is soluble in water, the tissue should be fixed in alcohol. The stable form occurs in minute quantity in many tissues, and under pathological conditions it may be greatly increased in amount. Glycogen is the only carbohydrate which can be demonstrated under the microscope, and is of particular interest on that account. It is colored reddish-brown with iodine, and is beautifully shown by Best's carmine stain which colors it crimson. After the use of watery fixatives (formalin) it appears as fine vacuoles. The liver cells of a person who has died a sudden accidental death are seen to have a foamy vacuolated appearance which is apt to be mistaken for a pathological condition. It is in reality the normal picture of a healthy liver, and is identical with the appearance seen in a piece of liver removed surgically, especially if the patient has received a preoperative injection of glucose. The liver seen in the ordinary hospital autopsy is one which is depleted of glycogen, as the patient is likely to have eaten little during the preceding twelve hours.

Under pathological conditions there may be an increase (infiltration) or diminution in the amount of glycogen in the tissues. In *diabetes* the depot glycogen is rapidly converted into glucose, so that there is



a marked diminution in the amount in the liver and muscles. For some reason the amount in the heart muscle is increased. Large deposits appear in the epithelium of the renal tubules, especially the loop of Henle (Fig. 5), probably owing to absorption of glucose from the sugar-loaded urine. In *suppurations* the polymorphonuclear leucocytes both in the blood and the pus contain an excess of glycogen (iodophilic granules). Glycogen is likely to appear in places which show a pathological increase of fat, and probably from similar causes. It is abundant in some *tumors*, especially in hypernephroma (a malignant tumor of the kidney), where the cells have a highly vacuolated or characteristically clear appearance, due to the presence of fat and glycogen, which are present in varying proportions.

**Glycogen Accumulation Disease or von Gierke's Disease.**—This is a strange condition in children, characterized by an excessive storage of glycogen, espe-



FIG. 5.—Glycogen represented by clear spaces in renal tubules in diabetes.  $\times 225$ .



FIG. 6.—Von Gierke's disease. Liver cells distended with glycogen, which has been dissolved out.  $\times 400$ .

cially in the liver and to a lesser degree in the kidney. The liver becomes enormous, and this great hepatomegaly in a child unaccompanied by splenomegaly, jaundice, or any marked constitutional disturbance is highly characteristic. There is hypoglycemia, but without the usual clinical symptoms. The injection of adrenalin fails to mobilize the glycogen in the liver as it should do in a normal person. Acetone and diacetic acid may be present in the urine but without glycosuria. The cause of this ketosis is fundamentally the same as that of diabetes, although brought about in a different way. In diabetes the sugar, although present in abundance in the blood, is unable to play its

proper part in the combustion of fats. In this disease the fats are not properly burnt because the sugar is held in the liver in the form of glycogen. The liver cells are greatly distended, the cytoplasm clear or vacuolated and, in one case which I studied, the cell boundaries in many places appeared to be broken down (Fig. 6). In von Gierke's original case the kidneys were markedly enlarged owing to accumulation of glycogen in the epithelium of the convoluted tubules. Pompe has described under the title of idiopathic hypertrophy of the heart a case of enormous enlargement of the heart in a young boy in whom the heart muscle fibers were hugely distended with glycogen. The disease appears to depend on a defective transformation of glycogen into glucose owing to absence of the normal glycogenolytic enzyme, so that it accumulates in the glycogen depots. The condition is, therefore, analogous to the lipid storage disease (Gaucher's disease, Niemann-Pick's disease, Christian's syndrome) in which the cells of the reticulo-endothelial system become loaded with lipid. Glycogen storage, like lipid storage, may show a familial tendency and may be regarded as a congenital anomaly of metabolism.

### AMYLOID DEGENERATION

A remarkably interesting though nowadays rather uncommon degenerative process is that known as amyloid degeneration. It differs fundamentally from fatty degeneration in that it affects connective-tissue fibers and not the parenchymatous cells of an organ, although the latter may undergo secondary changes.

**Nature of Amyloid.**—The name amyloid is singularly misleading. It was first suggested by Virchow because he thought that the substance was a carbohydrate allied to starch (*amylon*, starch), on account of the blue color produced when the amyloid material was treated with iodine followed by sulphuric acid. It is now known to be protein in nature, and appears to be a compound of albumen with chondroitin-sulphuric acid. The most characteristic of all the staining reactions, that with methyl violet, is dependent on the presence of this acid. It must be admitted, however, that one or two observers have failed to demonstrate the presence of the acid. Amyloid is a highly resistant substance, being unaffected by peptic digestion, insoluble in water, very slightly soluble in strong acids, but readily soluble in strong alkalis. The chemical composition varies somewhat, depending on the source of the amyloid. It does not occur normally in the body, but in marked forms of the disease it is present in enormous amounts in the affected organs. The question naturally arises: What is the source of the amyloid?

It seems fair to direct our attention to the chondroitin-sulphuric acid. As the name implies, the substance occurs principally in cartilage. It is also found in organs rich in elastic tissue such as the lung and aorta. Amyloid disease is commonly associated with long-continued destruction of such tissues, *e. g.*, chronic osteomyelitis, suppurative arthritis, and pulmonary tuberculosis. It might appear that chondroitin-sulphuric acid is liberated in these conditions and carried to the special sites in which amyloid tends to accumulate. Moreover, rare amyloid "tumors" are found in relation to the nasal septum, larynx, and bronchi, all of which are structures rich in cartilage. Unfortunately on further inquiry this explanation is found to break down somewhat, because amyloid may occur without any destruction of tissue, and may be produced experimentally by the injection of bacterial toxins and even by casein injections. Moreover, injections of chondroitin-sulphuric acid have never resulted in the formation of amyloid. If this explanation is inadequate, there appears to be no other to put in its place.

**Causes of Amyloid Disease.**—In the great majority of cases amyloid degeneration occurs in chronic cachectic conditions associated with

marked loss of albumen from the body. These conditions may be divided into three main groups: (1) Chronic tuberculosis of bones, joints, lungs, kidneys, bowel, especially when secondary infection is superadded. (2) Long-continued suppuration of bones and joints, chronic empyema, and other similar conditions in which there is prolonged suppuration with discharge of pus from the body. (3) Syphilitic lesions, either acquired or congenital, especially when associated with suppuration, *i. e.*, breaking-down gummata. As all of these conditions have become much rarer owing to modern methods of treatment, amyloid degeneration is no longer the common disease it once was. It is most likely to be seen in a tuberculosis sanatorium. In addition to these three main groups, a number of other conditions must be mentioned. Syphilis uncomplicated by suppuration may apparently act as a cause. It has been found associated with malignant tumors, malaria, dysentery, Hodgkin's disease, and repeated attacks of rheumatic fever. In multiple myeloma of bone masses of amyloid have been reported in the marrow and muscles. Sometimes no adequate cause can be found, as in a case of my own where the autopsy failed to reveal any explanation for the advanced general amyloidosis.

The experimental production of amyloidosis is interesting, though it cannot be said to have thrown much light on this dark subject. The condition can be produced in many different animals and in a variety of ways. The injection of bacterial toxins over a period of months may lead to amyloid degeneration, although by no means invariably. A broth culture of *Staphylococcus aureus* has been much used. Horses injected with diphtheria toxin for the production of antitoxin may develop amyloid. Mice with transplanted malignant tumors may show amyloidosis. The subcutaneous injection of nutrose (sodium caseinate) into mice, a method introduced by Kuczynski in 1923, is the most effective and rapid way of producing amyloidosis. Feeding the animal on a diet rich in cheese will produce the same result. These results with casein are of interest as showing that amyloid may be produced apart from bacteria and their toxins. Smetana obtained amyloid after seventeen daily injections of nutrose, and also after thirty days of feeding with cheese. One great advantage of the experimental method is that it is possible to study the condition of the tissues immediately before the appearance of the amyloid. The experimental amyloid is best stained by the intravenous injection of Congo red before the animal is killed. Tissue for paraffin embedding must be fixed in corrosive sublimate, not formalin, otherwise the color will be lost.

Lipoids may play a curious rôle in experimental amyloidosis. When white mice are painted with coal tar, amyloidosis may develop, but if the animal is at the same time fed on cholesterol and fat it generally remains free from amyloid. The cholesterol seems to be of much greater importance than the fat. The administration of a rich lipoid diet has a protective action against nutrose injections, twice as many injections being necessary to produce amyloidosis as in an animal on

normal diet. The fat diet must not be started later than the nutrose injections, otherwise it is useless. At first the liver is loaded with lipoids, owing to the rich diet; gradually the fat disappears, and its disappearance is soon followed by the appearance of amyloid. The mouse seems to be protected as long as it can store fat. Jaffé makes the wise suggestion that studies on cholesterol metabolism in man, completely lacking in the past, may throw more light on the nature of amyloid disease than elaborate chemical analysis of the amyloid itself.

**Staining Reactions.**—There are two special methods by which amyloid can be stained: (1) iodine, (2) methyl violet.

*Iodine* in watery solution, conveniently used in the form of Lugol's solution, stains amyloid a mahogany brown when viewed by reflected light, the surrounding tissue taking on a yellow color. The method is very useful in the autopsy room for determining if an organ contains amyloid; the solution of iodine is poured over the cut surface, and in a few minutes the dark brown patches of amyloid will appear. The renal glomeruli form a striking picture when the kidney is treated in this way. The method can be used for microscopic sections, the amyloid again appearing dark brown by reflected light, *i. e.*, when the mirror is not used. When viewed by ordinary transmitted light it is a pale orange. If the iodine is followed by 1 per cent sulphuric acid, the brown may turn a light blue. This reaction which is responsible for the name amyloid is quite variable. Moreover the reaction with iodine itself is often not given in the early stages of the disease, suggesting that the amyloid may undergo some chemical change as it matures. The iodine reaction is apt to fail in tissue which has been kept for a long time in formalin.

*Methyl violet* and gentian violet give a metachromatic reaction which is the best and most constant method of demonstrating amyloid. It acts well on tissue which has been kept long in formalin. With this method the amyloid stains a rose red due to the chondroitin-sulphuric acid, while the surrounding tissue is colored bluish violet. This metachromatic reaction is best obtained with frozen sections and is most clearly seen with artificial light.

*Congo red* stains amyloid in the living body. When this dye is injected into the blood stream of an animal with amyloid disease, all the amyloid is found to be stained bright red at autopsy. This method can be applied to the *clinical diagnosis* of doubtful cases, the amount of dye removed from the blood by the amyloid being measured at the end of an hour. When a 1 per cent solution of Congo red is injected intravenously, from 10 to 30 per cent of the dye will disappear from the blood at the end of an hour. If the patient has amyloid disease 60 per cent or more will disappear in the same period of time. By means of the Congo red test it has been shown that amyloid may be removed from an organ if the cause responsible for it can be removed. The dye can be used as a microscopic stain if the tissue is fixed in corrosive sublimate before staining.

**Changes in the Organs.**—Amyloid degeneration is a widespread condition very rarely confined to a single organ, and may well be called general amyloidosis. The organs chiefly affected are the liver, spleen, and kidney, the change usually beginning in the spleen. An additional group of three comprises the adrenals, the pancreas, and the intestinal mucous membrane. In addition to these almost every organ in the body may show some degree of change. It is the connective tissue of the organs, particularly the fibers in the media of the arterioles, which is attacked. The affected fibers undergo a hyaline homogeneous

swelling, so that the organ looks as if molten wax had been poured into the interstices and had hardened there. As a result of this swelling the parenchymatous cells become compressed and atrophic. The walls of the small vessels are thickened and their lumen may be greatly narrowed. The liver and spleen are enlarged, dense and elastic, resembling hard India rubber, the edges remaining hard and sharp in contrast to the rounded contours of the fatty liver. The cut surface is smooth, and has a translucent waxy appearance, so that the condition is sometimes known as waxy degeneration. In the kidney other degenerative changes complicate the picture, so that its gross appearance will be described separately.

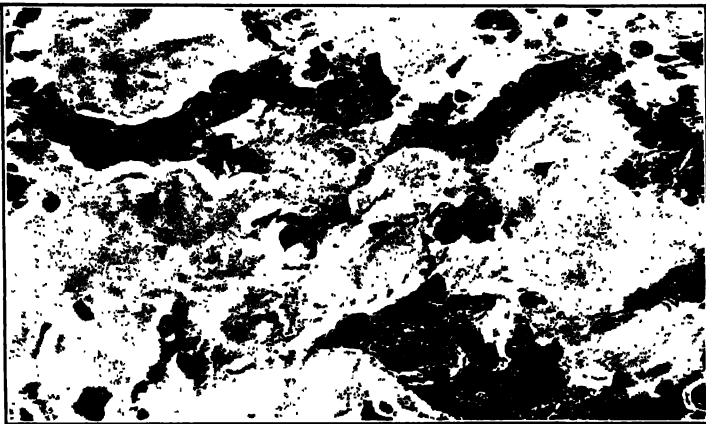


FIG. 7.—Amyloid degeneration of liver. The liver cells are greatly compressed by the abundant amyloid material.  $\times 350$ .

The *liver* is enlarged, sometimes to a great degree. It seems to have been fixed in formalin, so firm is its consistence and so sharply marked its borders, but it is elastic rather than hard. The cut surface presents the usual translucent appearance. Microscopically, the change commences in the intermediate zone of the lobule. The amyloid appears in the connective tissue between the sinus endothelium and the liver cells. This tissue becomes enormously swollen, so that on the one hand the liver cells are so compressed that they atrophy and may finally disappear, while on the other hand the sinusoids become narrowed. (Fig. 7.)

The *spleen* is also enlarged, firm, elastic, and translucent. The amyloid may be distributed in two ways. In the common form it appears in the walls of the arteries in the Malpighian bodies (Fig. 8) and these lymphoid masses are gradually replaced by translucent masses of amyloid which are scattered over the surface like grains of boiled sago, so that this form is known as the *sago spleen*. (Fig. 9.) In the rarer form, the *diffuse amyloid spleen*, the change affects the

connective tissue of the venous sinuses and the reticulum of the pulp, so that the enlargement of the organ is much greater.

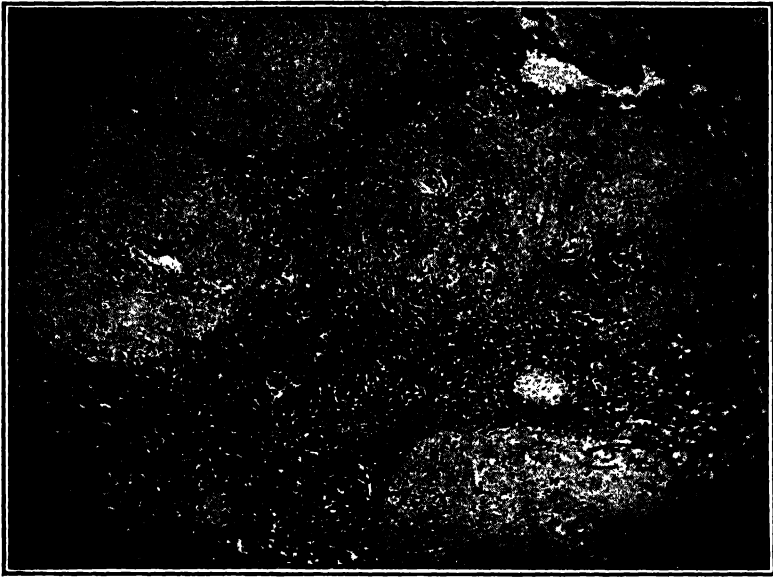


FIG. 8.—Sago spleen, showing large masses of amyloid.  $\times 45$ .

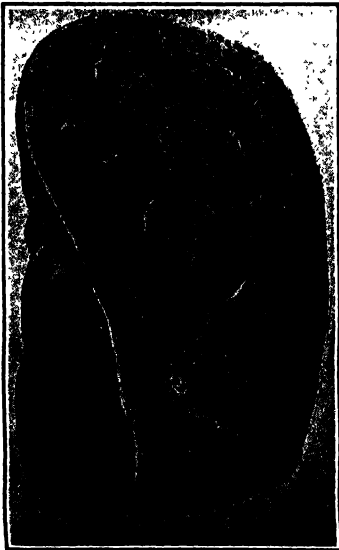


FIG. 9.—Amyloid spleen of the sago type. The numerous small areas of amyloid are stained darkly with iodine.

The *kidney* presents a special problem because of secondary changes. It may be enlarged like the liver and spleen, or normal in size, or even contracted. Fatty degenerative changes in the tubules are common, and these interfere with the waxy look of the cortex, giving it a streaked or spotty appearance. Microscopically the change begins in the connective tissue of the vessels in the glomerular tufts, and also involves the walls of the arterioles and the connective tissue under the basement membrane of the collecting tubules. When a solution of iodine is poured over the cut surface the affected glomeruli stand out as little brown dots. The glomeruli become converted into masses of amyloid, as a result of which all circulation through the glomerulus may be stopped, but usually some patent vessels still remain. Owing to

obstruction to the glomerular circulation the convoluted tubules are deprived of their blood supply and may undergo degenerative changes with great accumulation of lipoid, so that the condition has been unfortunately called amyloid nephrosis. It is these tubular changes which are responsible for the gross appearance already described. The tubules may gradually atrophy and be replaced by fibrous tissues, which by shrinking produces a picture of a contracted kidney like that of chronic Bright's disease. There is no real relation between amyloid degeneration and Bright's disease.

Many *other organs* may show the amyloid change. The adrenals may be converted into solid masses of amyloid so that they become considerably enlarged. In the intestine the change affects the connective tissue in the villi (Fig. 10), so that when treated with iodine the mucosa may have an appearance of brown velvet. The thyroid may be converted into an almost solid mass of amyloid. The heart may be the seat of extensive amyloid deposits between the muscle fibers. The heart cases fall into two groups. In the first and most numerous the cardiac deposits are merely part of a generalized amyloidosis, while in the second the amyloid is confined to the heart (primary myocardial amyloidosis). In addition to these principal sites, small deposits of amyloid may be found in almost any of the other organs. There may be widespread amyloidosis of the lymph nodes. In one obscure case of enlarged liver with palpable superficial lymph nodes I found amyloid in an excised node thereby enabling a correct diagnosis of amyloid degeneration of the liver to be made.



FIG. 10.—Amyloid degeneration of intestine. The villi are much enlarged by amyloid deposits.  $\times 60$ .

**Localized Amyloid Deposits.**—Amyloid may be deposited locally without any general amyloidosis. The instance of local myocardial deposits has just been cited. The lymph nodes draining an area of chronic suppuration may show similar deposits, suggesting the direct action of toxins on the local tissues. Peculiar amyloid masses known as amyloid "tumors" are rare occurrences in relation to the nasal septum, the larynx, and the bronchi. As all of these are cartilaginous structures it would appear that chondroitin-sulphuric acid may be liberated locally and converted into amyloid material. Amyloid deposits may also occur at the base of the tongue. Paige reports a case with huge tumor-like masses of amyloid in the muscles, in addition to involvement of the spleen, kidneys, gastro-intestinal tract, heart, pancreas, testes, sympathetic ganglia, and fat, but not the liver.

**Clinical Effects.**—General amyloidosis may or may not produce clinical effects. The organs of importance in this respect are the kidney and liver. The relation of amyloid disease of the kidney to nephritis has long been a subject of discussion. It has been maintained that the amyloid kidney is a form of nephrosis (Fahr), and also that it occurs in the course of chronic nephritis. It would seem nearer the truth to regard the amyloid change in the glomeruli as the primary lesion and the degeneration in the tubules as purely secondary. The kidney may be large or small, depending on how far the tubular change has gone before the patient died. The clinical picture may simulate or be identical with that of glomerulonephritis. Renal edema may be associated with albuminuria and casts, or there may be signs of renal insufficiency and nitrogenous retention, with polyuria and a urine of low specific gravity and little or no albumin. Vascular hypertension would be expected on account of the widespread narrowing of the capillary bed in the glomeruli, but for some unknown reason this is seldom observed. Amyloid disease of the kidney bears no relation to true Bright's disease, although it may simulate it both clinically and pathologically.

In the amyloid liver there is great narrowing or even obliteration of the sinusoids, so that ascites might be confidently expected. As a matter of fact this is so rare that one recent text-book of medicine denies its existence, but I have seen an extreme degree of ascites which rapidly reaccumulated after tapping in an advanced case of amyloid disease of the liver, in which that organ weighed over 2500 grams.

The watery diarrhea which sometimes accompanies amyloidosis may be due to increased transudation through the diseased intestinal mucous membrane.

The *Congo red test* is of great value in clinical diagnosis. Disappearance of over 60 per cent of the dye from the blood in one hour is found only in amyloid disease. This only applies to considerable deposits of amyloid, particularly in the liver. Deposits in the kidneys alone are not sufficient to give the typical reaction.

### HYALINE DEGENERATION

The changes grouped together as hyaline degeneration are in a very different category from fatty and amyloid degeneration. In the latter we are dealing with substances of a definite chemical composition, whereas in the former the composition varies widely in different cases. The term denotes a physical state rather than a chemical constitution, and includes many substances which are translucent or hyaline and stain brightly with acid dyes such as fuchsin. Hyaline degeneration affects chiefly collagenous connective tissue and the fibrous tissue in the walls of bloodvessels. This may be called connective-tissue hyaline. Other forms can be grouped together as cellular hyaline. The tissue dies before becoming changed into hyaline.



*Connective-tissue hyaline* appears as a homogeneous swelling of collagen and in the walls of vessels in arteriosclerosis. It is seen in chronic malnutrition and in old age, but the exact factors responsible are not certain. The change is well seen in arteriosclerosis. In the intima the newly-formed tissue undergoes a hyaline change, and a similar change may occur in the media. The subendothelial layer of the arterioles shows marked hyaline thickening in vascular hypertension. In chronic nephritis the renal glomeruli become converted into hyaline masses. Scar tissue undergoes a similar change. The stroma of tumors may show hyaline degeneration, and the same may be seen in the reticulum of lymph nodes draining a focus of chronic inflammation. (Fig. 11.)



FIG. 11.—Hyaline degeneration of a lymph node.  $\times 350$ .



FIG. 12.—Zenker's degeneration of muscle in typhoid fever. The affected parts of the fibers have lost their transverse striations and are dark and swollen.  $\times 400$

In all of these instances the fibrous tissue loses its structure, the fibers are swollen and homogeneous, and stain red with acid stains. The appearance may resemble that of amyloid, but the material does not give the amyloid staining reactions.

*Cellular hyaline* is a heterogeneous group with no special meaning. Small hyaline masses are often seen in the cells of the renal tubules, especially in amyloid disease. The cells of the islets of Langerhans in the pancreas may become converted into a hyaline mass in diabetes. Hyaline thrombi in vessels are formed largely by fusion together of blood platelets which then undergo hyaline degeneration. *Corpora*

*amylacea*, so called because like starch they stain deeply with iodine (*amylon*, starch), are hyaline spherical masses made up of concentric laminæ. They are seen in the normal prostate, in old infarcts of the lung, in the brain and spinal cord in old age and in degenerative conditions, and occasionally in other situations. They represent masses of degenerative cells and sometimes merely the secretion of cells. They stain deeply with hematoxylin, and have nothing to do with amyloid. In necrosis of voluntary muscle and sometimes of cardiac muscle the protoplasm may become coagulated, the striations are lost, and the fiber is converted into a swollen homogeneous hyaline mass. (Fig. 12.) This condition, known as *Zenker's degeneration*, is best seen in the rectus abdominis muscle in typhoid fever, but is also seen in other muscles and other infections.

### MUCOID DEGENERATION

Mucin is produced normally both by epithelial cells of mucous membranes and mucous glands and by certain connective-tissue cells, especially in the fetus. When the secretion of mucin is excessive and is associated with degeneration of the cells, the condition is called muroid degeneration.

**Epithelial Mucin.**—In catarrhal inflammation of the mucous membrane of the respiratory tract, the gastro-intestinal canal, and the uterus, there is an excessive secretion of mucin, the cells are distended with this substance, and their outlines may disappear. The cells of a cystadenoma of the ovary produce pseudomucin in enormous amount so that a huge cyst may be formed; many of these cells degenerate and are cast off into the cyst. Cancer of the stomach, the large bowel, and more rarely the breast may produce mucin to such an extent that the tumor is converted into a mass of muroid material. Such tumors are called colloid cancer, a bad term which should be changed to muroid or gelatinous cancer. Mucin is a slimy substance which is precipitated by acetic acid; it is basophilic, *i. e.*, stains with basic dyes, and gives a metachromatic reaction with toluidin blue, staining reddish-purple. Pseudomucin is not precipitated by acetic acid, and is stained by acid stains.

**Connective-tissue Mucin.**—The only place where intercellular connective-tissue mucin normally occurs is in the umbilical cord. The cells are stellate with branching processes and are separated by an abundance of clear mucin. This mucinoid or myxomatous degeneration may occur in the stroma of various tumors, most notably in the myxoma. In conditions of malnutrition a similar change may affect the bone-marrow, adipose tissue, and cartilage. In myxedema, a disease due to deficiency of thyroid secretion, the connective tissue of the skin and elsewhere becomes swollen and gelatinous, and in the early stages contains mucin. Mucin may be formed in the intercellular substance of synovial membranes and tendon sheaths; the development of this process is beautifully illustrated in the early stages of a ganglion of the wrist.

*Colloid degeneration* is a term found in the text-books, but it is of little practical value and would be better abandoned. The colloid of the thyroid is a secretion with a definite chemical composition which bears no relation to that of the colloid or glue-like substances occasionally found elsewhere. Colloid cancer, colloid casts of the kidney, etc., are undesirable terms; the name should be reserved for the secretion of the thyroid.

### GOUT

Gout is an ancient and famous disease. Its cause, however, is still a complete mystery. There is often a strong hereditary tendency. It

is supposed to be a disturbance of purine metabolism. In support of this are the following facts: (1) The uric acid of the blood is above normal, and for a few days before an acute attack there is marked uric acid retention. (2) Deposits of sodium urate are a principal feature of the lesions. (3) Overindulgence in purine-rich foods often precipitates the attacks. Beer and such red wines as port are much more dangerous than whisky; perhaps for this reason gout is a rare disease in Scotland. These facts do not constitute proof, for the blood uric acid may be equally high in leukemia and chronic nephritis, the deposits of urates are present in the joints when the patient is free from symptoms, and the acute attack may come on without obvious cause. The deposits of urates and the high blood uric acid may be merely concomitants of the disease, perhaps a result rather than a cause.

Gout may occur in chronic form, or as a series of acute attacks, each of which begins as agonizing pain in a joint, usually at night, followed by fever and chills; the joint is swollen, tender, and evidently acutely inflamed, and the blood may show a leucocytosis of 20,000 or more. It must be admitted that to be unable to offer a reasonable explanation for so dramatic a picture is unsatisfactory if not humiliating.

The joints chiefly affected are those of the big toe (metatarsophalangeal joint) and fingers and the knee-joint. In the superficial layers of the articular cartilage there are white chalky deposits of biurate of sodium rather like drops of paint, an appearance from which the name gout is derived (*gutta*, a drop). The sheaves of needle-shaped crystals are usually surrounded by an area of necrosis. It is not certain whether the necrosis precedes or follows the deposition of the crystals.

Accumulations of crystals may also occur in the periarticular tissue where they form masses known as tophi. Around these may often be seen foreign body giant cells. Similar deposits occur in the cartilage of the ear and in the eyelid. The overlying skin may become ulcerated and chalky material is discharged containing the characteristic crystals. A useful diagnostic procedure is to prick a suspected tophus with a needle, and look for the crystals under the microscope. Deposits of crystals may occur in the pyramids of the kidney, for the most part within the collecting tubules but also between them, giving the pyramids a streaked appearance.

## PATHOLOGICAL PIGMENTATION

The group of substances known as pigments have nothing in common save that they are colored, but it is convenient to consider them together. They may be produced within the body (endogenous pigments) or introduced from without (exogenous pigments). There are three chief groups of endogenous pigments: (1) melanins, (2) lipochromes, and (3) derivatives of hemoglobin. Pigment metabolism may become pathological owing either to over-production or under-production.

**Melanosis.**—Melanin is the coloring matter of the skin, the hair, the iris, and the choroid coat of the eye. It also occurs in the medulla and zona reticularis of the adrenal and in certain parts of the central nervous system. In animals, pigment plays an important rôle as a means of attraction and of defensive mimicry. It possesses remarkable power of movement as shown by the rapid changes in color in the skin of a chameleon. The pigment or rather the cells containing the pigment can pass from the superficial to the deep layers of the skin and back again. Some animals produce large quantities of melanin, notably the cuttlefish whose ink-sac is lined by cells capable of manufacturing huge quantities of the pigment.

In man the normal amount of melanin in the skin is very small. It is much greater in the negro than in the white man, but even in the former the entire skin does not contain more than 1 gram of pigment. In the tumor known as the malignant melanoma as much as 300 grams of melanin have been removed from the liver alone, so that under some conditions the pigment-forming power of the body is greatly increased. As the result of inflammation of the skin the melanin may become mobilized and transported to the regional lymph nodes, where it is contained in phagocytic histiocytes. In one case which I studied the possibility of malignant melanoma had been considered. In man the function of melanin appears to be to serve as a protection against strong actinic light; hence the deepened color of the skin when exposed to sunlight and the intense color in the negro. It is of interest to note that skin cancer is very uncommon among colored races.

The composition of melanin is still unsettled. It is a derivative of protein, and is stated by almost every book to contain sulphur, sometimes in large quantity, but Brahn has shown by more exact methods that sulphur is usually absent. The aromatic compounds of the protein molecule, tyrosin, phenylalanine, and tryptophane, are readily oxidized with the production of a dark color. It is probable that the chromogen groups of the protein molecule may be acted on in a similar manner by an oxidizing enzyme in certain cells to form the brown or blackish melanin. Such an oxidizing enzyme, tyrosinase, is found in the ink-sac of the cuttlefish, and can form melanin from tyrosin and other aromatic compounds. Adrenalin is also an aromatic derivative, and is probably formed from the same mother substances as melanin. The effect of melanin on the bloodvessels of a frog is very similar to that of adrenalin. The actual course of events in the formation of melanin appears to be somewhat as follows: Owing to the action of autolytic enzymes the aromatic or chromogen groups are split free from the protein molecule; these are oxidized by the intracellular tyrosinase, minute quantities of iron or sulphur may be added, and melanin is deposited within the cytoplasm where it appears in the form of granules.

The pigment is formed by cellular activity. Intercalated among the basal cells of the Malpighian layer of the skin are peculiar branched cells which produce an oxydase ferment capable of transforming the

colorless chromogenic material in the blood into melanin, so that these cells may be called *melanoblasts*. Some of the pigment is transferred to connective-tissue cells in the dermis; as these cells are mere carriers of the pigment they are called melanophores or *chromatophores* (*phoreo*, I carry). The most important recent work on the chemical side is that of Bloch. He has shown that dihydroxyphenylalanine (shortened to "dopa") reacts with an oxydase in certain cells of pigmented regions to produce a dark material closely related to melanin. This "*dopa*" reaction indicates those cells which are true melanoblasts and contain the ferment. In frozen sections of the skin many basal cells of the epidermis are found to be "dopa"-positive, while the mesodermal cells are "dopa"-negative. Melanoblasts are "dopa"-positive, chromatophores are "dopa"-negative. "Dopa" appears to be closely related to the mother substance of melanin which is brought to the cells by the blood and converted into melanin by the ferment. It seems probable that this mother substance or melanogen is the same both for melanin and adrenalin. In Addison's disease, due to destruction of both adrenals, adrenalin can no longer be formed, so that the excess melanogen may well be converted into melanin in the skin. Excellent summaries of Bloch's work will be found in the papers by Dawson, Spencer, and Laidlaw.

Under pathological conditions too much melanin may be formed or too little. The chief examples of too much pigmentation are the melanotic tumors, Addison's disease, melanosis of the colon, and chloasma. Ochronosis is related to melanosis. The increase of melanin in sunburn and freckles may be regarded as physiological. Diminished formation of melanin is seen in albinism and leucoderma. When too much melanin is formed it is excreted in the urine. In Addison's disease and melanotic tumors the kidneys often contain much melanin in the epithelial cells of the loop of Henle and the collecting tubules. The pigment granules are argyrophilic and can, therefore, be demonstrated by silver staining. (Renal casts containing melanin may be present in the urine, a point of value in doubtful cases of Addison's disease (Jacobsen).) In melanotic conditions the pigment can also be demonstrated by silver staining in the reticulo-endothelial cells of the liver, spleen, and lymph nodes.

*Melanotic tumors* are considered in detail in the section on Tumors, so that a mere outline must suffice here. The tumor may be innocent (mole or *nævus*) or malignant (malignant melanoma or melanotic sarcoma). The vexed question of the origin of these tumors will not be entered into here. Suffice it to say that the tumors contain melanoblasts, and therefore arise in such pigmented areas as the skin and the choroid. Curiously enough, pigmented tumors are common in white and gray horses but quite rare in dark horses. It is said that if a white horse lives long enough it is almost certain to die of melanoma. The malignant tumors contain far the most pigment. Many of the cells are loaded with melanin which under the microscope appears as yellow or brown (not black) granules, though the tumor is black to the naked

eye. Large numbers of the cells are not pigmented. The tumor cells are rich in oxydase, as shown by the "dopa" reaction. In the secondary growths the tumor cells continue to form pigment in enormous quantities. As much as 300 grams of pigment have been extracted from a melanotic liver. It is said that a farmer could paint his fences with the pigment from the melanotic tumors in a white horse. In rapidly growing tumors the pigment may escape into the blood (melanemia), and be excreted in the urine (melanuria). In rare cases there is a diffuse staining of the lining cells of the bloodvessels and the serous membranes. The melanin is excreted in the urine sometimes as colored matter, sometimes in a colorless form, having been reduced and decolorized probably in the liver; on exposure to the air the melanogen again becomes oxidized into melanin. When melanin is injected intravenously it may appear in the urine either in colored or colorless form.

*Addison's disease* is considered in the section on the Adrenals. Owing to disease of the adrenals, usually tuberculosis, the skin becomes deeply pigmented especially in the parts exposed to light (face and hands), and in regions already pigmented (areola of nipple, axilla, scrotum). Patches of pigment on the gums may be present and are of diagnostic value in the negro. The pigment is in the form of fine granules in the epithelial cells of the deeper layer of the epidermis, and coarser granules in the chromatophores in the cutis vera. The pigment appears to be identical with melanin. As the chromogen or mother substance appears to be the same for adrenalin as for melanin, it seems likely that the surplus of this substance which can no longer be used by the diseased adrenal is carried to the skin and converted by the oxydase of the melanoblasts into melanin. The bronzing of the skin must be distinguished from that of hemochromatosis (bronzed diabetes), in which the pigment is iron.

*Melanosis coli* is a condition in which a black pigment, either melanin or closely related to melanin, is deposited in the mucous membrane of the large intestine and appendix. Like so many other pathological states, it was first described by Virchow. The extreme grades are comparatively rare, but if the slighter forms are included the incidence is fairly high. Stewart and Hickman found it in 11.2 per cent of 600 autopsies. The incidence is higher in those over middle age, and much higher in carcinoma of the colon. Melanosis of the appendix may occur apart from any pigmentation of the colon; it may be seen in appendices removed at operation. The coloration which varies from gray to inky black can be seen through the intestinal wall, and is sharply limited by the ileocecal valve. In advanced cases there may be metastases of pigment to the submucosa and the mesocolic lymph nodes. The granules of pigment are found within large mononuclear cells in the stroma of the mucous membrane; the epithelium is not affected. The condition is often associated with chronic intestinal stasis either from organic obstruction or simple constipation. The pigmented cells are dopa-negative, and are, therefore, melanophores that have taken up pigment which has either been ingested in the food or synthesized in the bowel.

**Ochronosis.**—This very rare condition was given its name by Virchow because of the ochre color which the nose and ears may present (*ochros*, sallow). There is a blackish discoloration of the cartilages, and sometimes of connective tissue, sclerotics, muscles, and epithelial cells. When the cartilages are sub-

cutaneous (nose, ear), the color may shine through the skin. The pigment may be deposited in the kidneys. In the only case which I have seen, the pyramids of the kidneys and the choroid plexus of the lateral ventricles were a startling black color. The skin of this patient was a peculiar gray, as if it had been black-leaded. The pigment is either melanin or closely related to that substance. In a majority of the cases reported there has been marked alkaptonuria. In a few cases there has been prolonged use of carbolic acid dressings. It is supposed that the pigmentation is due to the action of tyrosinase on aromatic protein decomposition products (tyrosin, phenylalanine, etc.), or phenol derivatives in the carbolic acid cases.

Other examples of melanosis or pigmentation in which a melanin-like substance is formed can only be mentioned. *Chloasma* is a condition in which brown patches appear in the skin of the face and elsewhere. They are seen in pregnancy and diseases of the uterus and ovaries, tuberculosis, Graves' disease, and following the application of heat (hot-water bottles). In cachexia the skin often shows patches of pigmentation. If such a patch be excised it will be found to give a marked "dopa" reaction. The body louse injects a fluid which produces a black spot of melanin in the deepest layers of the epidermis. An emulsion of the insect's salivary glands has the same effect when injected.

*Absence of melanin* is much rarer than excess of the pigment. *Albinism* is a congenital absence of melanin, which may be partial or complete. In *leucoderma* there are white patches of skin as the name implies, due usually to a process of depigmentation; a section of such a patch is negative to the "dopa" reaction, suggesting that the cells are lacking in the specific ferment. White patches of skin are found in leprosy, due apparently to interference with the nerve supply. The bleaching of hair is due to a loss of melanin. The white winter fur of arctic animals contains no melanin.

**Lipochromes.**—The colored fats form a loose group regarding which little is known. They are yellowish granules found in the heart muscle, nerve cells, seminal vesicles, adrenal cortex, corpus luteum, and interstitial cells of the testis. They have been called "wear and tear" pigments, being apparently produced from the cytoplasm in the process of wasting. The best example is *brown atrophy of the heart*, a wasting of the myocardial fibers seen in old age and cachectic disease conditions, and accompanied by a great collection of brown granules in the muscle fibers at either pole of the nucleus. These granules, which are normally present in small amount, stain red with Sudan. Similar granules are seen in the nerve cells, especially the large cells of the cerebral cortex, in senile and mental conditions. Some of these pigments may belong to the group of *plant pigments* (carotin and xanthophyll) found in carrots and other vegetables, egg-yolk, etc. If a person eats too many carrots he may develop *carotinemia*, with bright yellow coloration of the blood serum, the palms of the hands, and the nasolabial folds. The condition is sometimes seen in diabetes.

**Hematogenous Pigmentation.**—The red blood corpuscles are continually being destroyed in health. In disease this process may be greatly increased. The destruction may be local as in a hemorrhage, or general as in hemolytic diseases. Hemoglobin contains iron, but does not give an iron reaction with the ordinary tests. When it is broken down two moieties are found: the one, hematin, is iron-free, while the other, hemosiderin, contains iron and gives the iron

reaction. The iron-free portion is converted into bilirubin, and excreted in the bile, but the iron of the hemosiderin is too valuable to be lost and is retained within the body to be built up again into hemoglobin.

*Hematoidin.*—Hematoidin may assume the form of brown rhombic crystals or of amorphous granules seen in the neighborhood of any old hemorrhage. The granules are usually extracellular, but may also be found within phagocytic cells. Hematoidin is identical with bilirubin, and is excreted as such in the bile. In conditions of increased hemolysis there is therefore an increased formation of bilirubin; this may accumulate in the blood and stain the tissues yellow, giving rise to that form of jaundice known as hemolytic jaundice. When the van den Bergh test for bilirubin is applied to local and not too recent extravasations of blood, a positive reaction is obtained. It is only when the hemorrhage is large and absorption is imperfect that the pigment is deposited in solid form. In small hemorrhages the pigments are soluble and stain the surrounding tissue with the familiar color of a bruise.

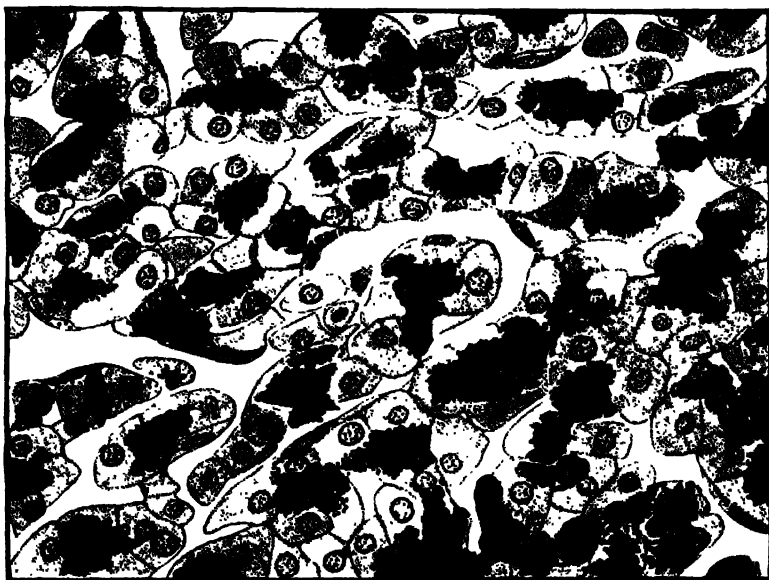
*Hemosiderin.*—Hemosiderin, the iron-containing pigment, gives the Prussian blue reaction for iron with potassium ferrocyanide and hydrochloric acid. This test may be applied either to microscopic sections or to the gross specimen. The pigment takes the form of fine yellowish-brown crystals which are usually contained within cells. Hemosiderin, therefore, is chiefly intracellular, hematoidin chiefly extracellular. The hemosiderin may be formed as the result of hemorrhage or of general hemolysis. In the former the hemosiderosis is local, in the latter it is widespread. The reticulo-endothelial system is intimately connected with hemosiderosis in three different ways: (1) The pigment-filled cells which surround an old hemorrhage are histiocytes belonging to this group. (2) Certain hemolytic diseases, *e. g.*, hemolytic jaundice, are dependent on the activity of the reticulo-endothelial system; the hemolysis is followed by the deposition of hemosiderin. (3) General hemolysis may be due to some extraneous source such as snake venom, but again hemosiderin is found within the reticulo-endothelial cells.

Hemolysis from whatever cause is therefore likely to be followed by hemosiderosis. The pigment is not only found in the reticulo-endothelial cells, but also in the epithelial cells of the liver and kidney. A marked Prussian blue reaction is obtained in those cells in pernicious anemia. Hemolysis is always accompanied by an increased formation of bilirubin. When this is marked it can readily be detected in the blood, it stains the tissues, but does not escape in the urine. In the curious condition of paroxysmal hemoglobinuria there is marked hemosiderosis of the liver and the cells of the convoluted tubules of the kidney as the result of the increased destruction of blood.

There may be an increase in the iron content of certain tissues, and yet the iron may not be demonstrable by ordinary histological methods. This invisible iron can now be demonstrated microscopically (Popoff). It is readily detached from the erythrocytes, and is rapidly taken up by mesenchymal and epithelial cells. Siderosis due to this cause is



## PLATE II



**Liver Showing Hemochromatosis.**

Prussian-blue reaction for iron. The hemosiderin granules are present mainly in the liver cells and to a lesser degree in the Kupffer cells.



seen in hemolytic and other conditions, but it is especially striking in congestive heart failure, in which practically all the septal cells of the lung may be seen to be loaded with iron granules instead of a mere sprinkling of phagocytes containing hemosiderin.

**Malarial Pigmentation.**—The malaria parasite within the red blood cells forms a dark brown pigment which is liberated with the destruction of the red cells and deposited in large quantities in the spleen and liver. This pigment does not give the Prussian blue reaction and at one time it was believed to be melanin, but it contains iron. Hemosiderin may also be deposited in addition to the malarial pigment.

**Hemochromatosis.**—This rare disease, also called *bronzed diabetes*, is a disorder of iron metabolism, but its exact nature is still a mystery. The normal amount of iron in the body is only 2.5 grams, but in this disease the liver alone may contain 30 grams or more. (Plate II.) The pancreas also contains large amounts of iron. Smaller quantities are found in the kidneys, adrenals, spleen, heart and voluntary muscles, thyroid, skin, and lymph nodes in the upper abdomen. The organs containing the pigment have a brown color (hence the name of the disease), and the skin is bronzed (*bronzed diabetes*); much of the pigment in the skin appears to be melanin. The affected organs give a vivid Prussian blue reaction.

One of the great problems is the source of the iron pigment. The name of the disease suggests that the iron is derived from the blood, and the experimental work of Mallory on experimental chronic copper poisoning was believed to indicate that as the result of slow hemolysis iron was carried from the blood to the liver by copper and stored there. It should be noted that anemia is not present, as might be expected if there was continued blood destruction. It is true that pigment cirrhosis of the liver can be produced in rabbits by long-continued administration of copper (Mallory and others), but pigment cirrhosis is not the same thing as the generalized disease hemochromatosis. The more probable explanation is that there is some fundamental defect in iron metabolism. Sheldon, whose splendid monograph should be consulted, is of the opinion that this defect is inborn and inherited. The work of Gillman and Gillman, on the other hand, indicates that at least in some cases the disturbance may be nutritional in origin. These workers, in an investigation of the deficiency disease pellagra in South African negroes by means of repeated liver puncture, were able to demonstrate a series of changes in the liver cells beginning with fatty degeneration and ending with massive accumulations of iron identical with those seen in hemochromatosis. They believe that in their clinical material one of the commonest sequels of pellagra is hemochromatosis. The iron appeared to develop in or from the mitochondria of the liver cells. The condition should be called cytosiderosis rather than hemochromatosis. In addition to the iron pigment there is another pigment known as hemofuscin which does not give the iron reaction with Perles' stain. Gillman and Gillman believe this to be lipoidal in character, and suggest the preferable name cytolipochrome. It also appears to be derived from breakdown of the mitochondria.

The liver cells slowly undergo necrosis, and marked cirrhosis may develop, which constitutes one of the most serious features of the disease. In the pancreas destruction of the islets of Langerhans as well as of the acinar tissue takes place, and glycosuria develops (*bronzed diabetes*).

**Siderosis of the Globus Pallidus.**—The globus pallidus of the lenticular nucleus usually gives a marked iron reaction, due to the presence of iron in the walls of the vessels in this region of the brain. The condition has been mistaken by many workers (including the writer) for calcification owing to the dark blue staining with hematoxylin. (Fig. 13.) The walls of the vessels are infiltrated with iron salts which appear to be derived from the nucleus itself. The iron is seemingly not hematogenous in origin, and there is no increase in conditions of undue hemolysis. Hadfield considers that pallidal

siderosis is the expression of a slow involutory atrophy affecting the lenticular nucleus in at least 60 per cent of persons over the age of thirty years. I have described the condition as being characteristic of chronic epidemic encephalitis, but this apparently was a mistake. It appears to predispose to the acute bilateral necrosis of the lenticular nuclei which is so often seen in carbon monoxide poisoning.

**Biliary Pigmentation.**—The subject of jaundice is considered in detail in the section on the liver. The pigments of the bile are formed from the blood. When red blood cells are broken down either in health or as the result of disease hematoidin is formed which is identical with bilirubin. The bilirubin is formed not by the epithelial cells of the liver, but by the reticulo-endothelial cells in the liver (Kupffer cells) and throughout the body. The hepatic cells merely excrete the pigment, passing it from the blood into the bile ducts. If bilirubin accumulates in the blood the tissues become stained. The skin and whites of the eyes appear yellow, and the patient is said to be jaundiced. It is evident that bilirubin may accumulate in the blood for two reasons: (1) It may not be excreted owing either to an obstruction in the course of the bile passages or to sickness on the part of the liver cells; (2) it may be produced in excessive amount owing to undue hemolysis.

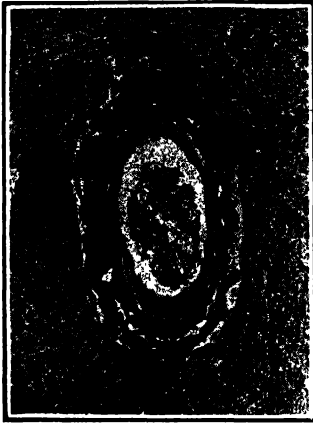


FIG. 13.—Iron in vessel wall in lenticular nucleus.  $\times 150$ .

The former is called obstructive jaundice, the latter hemolytic jaundice.

For a few days after birth the bilirubin of the blood is always above normal, and definite jaundice may develop. This is known as *icterus neonatorum*, and the bilirubin is hemolytic in type. The new-born child has a polycythemia, because the fetus lives in a constant condition of oxygen want and therefore needs a greater number of red blood cells to carry the oxygen to the tissues. After birth many of these cells are no longer needed and are broken down with the formation of bilirubin. The pigment may be deposited in the form of needle-like or rhombic crystals of hematoidin in the pyramids both in the collecting tubules and the interstitial tissue; these masses of pigment are called *bilirubin infarcts*.

**Exogenous Pigmentation.**—Pigments may be introduced from without and be deposited in the body. This introduction may occur through the respiratory tract, the alimentary canal, and the skin.

Through the *respiratory tract* dusts may be inhaled and deposited in the lungs, where they cause varying degrees of chronic irritation, a condition known as pneumokoniosis. Of these dusts the only two of importance are silica (in gold-miners and stone-masons) causing sili-

cosis, and coal dust (in coal-miners) causing anthracosis. These diseases are considered in the section on the Lungs.

*Alimentary canal* pigmentation is of much less importance. The two most important examples are silver and lead. Long-continued administration of silver salts may give rise to a condition of *argyria*. The silver is deposited as an insoluble albuminate in the form of fine granules. The skin and conjunctiva may assume an ashen-gray color, and there is pigmentation of the internal organs. The pigment causes no disturbance, but the importance of the condition lies in the fact that the coloration of the skin is permanent, so that the face has an ashen appearance for the rest of the patient's life. The pigment is not intracellular, but seems to lie in the cement substance. In the skin it is found in the corium just under the epithelium and around the sweat and sebaceous glands. In the kidney it is chiefly in the glomeruli and outside the epithelium of the tubules. In other organs the distribution is similar.

Lead poisoning or *plumbism* is considered in the section on the Action of Poisons. Pigmentation of the gums is a common sign. The lead is absorbed from the alimentary canal or may pass through the skin. It circulates in the form of a soluble salt, and when this comes in contact with hydrogen sulphide formed from decomposing food around diseased teeth, lead sulphide is formed and deposited in the gum where it gives a characteristic "blue line."

Pigment is introduced through *the skin* in the process of tattooing. It is taken up by histiocytes and is lodged permanently in the connective-tissue spaces. None is found in the epithelium. Some of the pigment is carried by phagocytes to the lymph nodes where it is deposited.

## DISORDERS OF CALCIUM METABOLISM. CALCIFICATION

The occurrence of pathological calcification, the deposition of calcium salts in tissues other than bone, has been known for centuries, but during the last few years a flood of light has been thrown on general disturbances of calcium metabolism and on a number of diseases in particular. Calcium is one of the elements which is essential to life. The average blood calcium in health is 10 mg. per 100 cc. of blood and remains remarkably constant. Salts of calcium are deposited in the tissues: (1) In the normal process known as the ossification of bone; (2) in the pathological process known as calcification. The composition of the calcareous deposits in both processes is extraordinarily similar, there being about 9 parts of calcium phosphate to 1 part of calcium carbonate. In *ossification* the salts are deposited diffusely in specially prepared osteoid tissue which has a definite architecture and the cells of which exercise a controlling influence on the process so that they are called osteoblasts. In *calcification* the same salts are deposited as clumps of granules in tissue which is either dying or dead and from which all cells have disappeared. In both the proportion of carbonate to phosphate is so constant that it would appear as if a calcium carbonate-phosphate complex is first formed from which the individual salts are precipitated.

In thinking of the skeleton we are too apt to think of it in terms of the dead body as something fixed and immutable. This is a profound mistake. Not only are the bones the rigid framework of the body, they are also a great reservoir of calcium and phosphate, which may be drawn upon and depleted in accordance with the needs of

the body. During pregnancy the bones of the fetus have to be built up and the calcium needed is taken from the bones of the mother as well as from the food. During lactation there is a continued loss of calcium from the body, and if a cow be kept on a calcium-low diet the deficit is made up from the bones. In such diseases as osteomalacia in which there is marked decalcification of the skeleton there may be deposits of lime in other tissues, a condition known as *metastatic calcification*. The minerals of bone are thus in a constant state of flux.

There are two great regulators of calcium metabolism. These are vitamin D and the parathyroid secretion. Whether these work independently or in what way they are related we do not know. The action of vitamin D and its relation to cholesterol, ergosterol, and ultra-violet light will be discussed in the section on Vitamins. Suffice it to say here that this vitamin serves to regulate the exchange of calcium between the bones and the blood. When it is deficient in the diet of young children or when the food is lacking in lime the bones develop the changes characteristic of rickets. The parathyroid glands, as Collip has shown, also exert an all-important influence on calcium exchanges. Injection of an extract of the gland causes a marked rise in the blood calcium, this rise taking place at the expense of the calcium in the bones, another illustration of the fact that the minerals of bone are not in a static condition but in a state of flux. If the extract is continued until the blood calcium has reached twice its normal level, the animal will develop hematuria and melena, and will die in a state of coma. Removal of the parathyroids is followed by a great drop in the blood calcium and the development of tetany.

Several diseases are associated with a disturbance in calcium metabolism, mostly in the nature of a hypocalcemia. Rickets and osteomalacia will be discussed in relation to diseases of bone, and so need only be mentioned here. In *rickets* there is a serious disturbance of the normal process of ossification in the growing bones of children, accompanied by other disturbances and dependent on a deficiency of calcium or phosphate or vitamin D in the diet. It can be cured by the administration of vitamin D in the form of cod-liver oil or by ultra-violet light, the action of which on the ergosterol of the skin serves to convert it into vitamin D. *Osteomalacia* is a disease of adults characterized by marked decalcification and softening of the skeleton followed by the development of bone deformities. This also appears to be a deficiency disease, and may be regarded as an adult form of rickets. The parathyroids may be enlarged, but this appears to be a compensatory hyperplasia and not the cause of the osteomalacia as is believed by many. *Tumors of the parathyroids* may cause marked decalcification of the bones, a condition known as *osteitis fibrosa cystica*. The effect of these parathyroid tumors is very remarkable. The blood is flooded with calcium, but much of it is excreted in the urine. The calcium removed from the bones may be deposited in the kidney to form renal calculi or in the walls of the arteries. A curious feature is the development of tumor-like swellings in connection with the bones,

giving the microscopic picture of giant cell tumor of bone. These matters are discussed in detail in Chapter XXXII. *Tetany* is a manifestation of calcium deficiency characterized by a hyperexcitability of the nerve-muscle system. An excess of calcium ions or of hydrogen ions tends to depress this system, while a deficiency in these ions leads to hyperexcitability. Tetany may be induced by anything which lowers unduly the blood calcium, by parathyroid deficiency, rickets, over-ventilation of the lungs (with undue loss of carbon dioxide), pyloric stenosis (with undue loss of hydrochloric acid by continuous vomiting), or by feeding large amounts of sodium bicarbonate—in a word, by anything which leads to a low blood calcium or tissue alkalosis. The presence of calcium is necessary for the clotting of blood. For long it was believed that the failure of the blood to clot in jaundice was due to removal of calcium by bile salts, but it is now known to be due to absence of vitamin K.

**Calcification.**—Pathological calcification may occur as the result of the blood being flooded with calcium. This may be induced by repeated injections of parathyroid extract, or it may occur in such decalcifying diseases as osteomalacia, general carcinomatosis of bone, and multiple myeloma. The calcium is removed from the bones and deposited in other tissues. This variety is therefore known as *metastatic calcification*. The lime is deposited chiefly in the lungs, kidneys, and the mucous membrane of the stomach, probably in the living cells. The reason for the deposition is the hypercalcemia, not any degeneration on the part of the tissues involved. Enormous single doses of irradiated ergosterol (vitamin D) will produce massive calcification in the aorta, coronary arteries and heart muscle of the rat in forty-eight hours (Ham). At the end of twenty-four hours there is no indication in the tissues that a catastrophe is imminent, so that the chief factor in this case seems to be the inability of the serum to retain the calcium salts rather than degeneration on the part of the tissues.

It is much more common for the calcium to be laid down in dying or dead tissue without any reference to the blood calcium. Both phosphate and carbonate are deposited in practically the same proportion as is found in bone. The salts are soluble in weak acids, bubbles of carbon dioxide being given off owing to the presence of carbonates. The lime is stained blue with hematoxylin and black with silver nitrate. The mechanism by which the calcification occurs has long been a matter of dispute. According to Klotz there is first fatty degeneration; the fat is hydrolyzed with the liberation of a fatty acid; the calcium unites with the fatty acid to form a calcium soap; the fatty acid is then replaced by the carbonic acid and phosphoric acid in the blood, and the final result is calcium carbonate and calcium phosphate. Wells fails to find any evidence of the formation of a soap, and regards the process as a physical rather than a chemical one, the calcium and phosphate being adsorbed by the degenerated tissue. He found that pieces of sterilized cartilage placed in the peritoneal cavity of a rabbit soon became calcified, having taken up the lime from the fluid in which

they were bathed. It is probable that there is truth in both views. The areas of fat necrosis which result from acute pancreatitis may show striking calcification, and the same change may occur in a degenerating lipoma. In these cases it seems likely that Klotz's view is correct. There is, however, a tendency for any dying or dead tissue surrounded by living tissue and accessible to the body fluids to become calcified. In such necrotic areas circulation is absent, but a slow diffusion takes place from the surrounding blood and lymph. The dying tissue undergoes a hyaline change, and it is this hyaline material in which the carbon dioxide tension is probably low owing to tissue inactivity that becomes the seat of calcification. Necrosis and hyaline changes are the two chief antecedents of calcification. The physical rather than the chemical structure, as Wells remarks, seems to determine the deposition of the calcium.

Endless examples of calcification could be given, but a few will suffice. *Caseous tuberculous areas*, especially in the lungs and lymph nodes, frequently become calcified. The change usually indicates that the infection has died out and healing has occurred. In one form of *arteriosclerosis* (atheroma) the intima of the vessel develops calcareous patches (here preceded by fatty changes), in another form the media of the arteries to the limbs is affected. *Valves of the heart* which have been injured by previous inflammation are often calcified. Lime salts are often deposited in an *old abscess* in which the pus has become inspissated. A long-standing *empyema* or *pericarditis* may undergo the same change, so that calcareous patches are formed over the lung or the heart. A *thrombus* in a vessel may be calcified; such stony nodules, known as *phleboliths*, are often detected in the pelvic veins in roentgen-ray films. *Degenerating tumors*, especially fibroid tumors of the uterus, may become converted into masses of stone. In old age the *cartilages of the ribs* and the trachea are often calcified. A fetus which escapes into the abdominal cavity from a tubal pregnancy may become a *lithopedion*, a calcified fetus. A coating of lime may be formed over *animal parasites* in the tissues, particularly *Trichina spiralis* and *echinococcus* cysts. *Dead ganglion cells* in the brain may become encrusted with lime, so that a perfect cast of each cell may be formed. A peculiar example which deserves special mention is the calcification of the *convoluted tubules of the kidney* which rapidly develops after corrosive sublimate poisoning; here the calcium is deposited in the necrotic cells. It may be noted that even brief obstruction of the renal artery in the rabbit is followed by extensive calcification of the kidney.

## NECROSIS

By necrosis is meant the local death of cells. Now although death may be regarded as the final degeneration, a cell which has been suddenly killed shows no sign of degeneration. It looks exactly like a normal one. This after all is natural, for the fixed cells of microscopic



sections have all been killed. The cellular changes characteristic of necrosis are changes which the cell undergoes *after* it has died while still remaining in the body. These changes are very similar to those undergone by living cells when they are removed from the body and allowed to die, being due to the same cause, namely, the action of enzymes. It is evident that necrotic changes may easily be confused with those of postmortem degeneration, and the distinction is sometimes hard to make. The term *necrobiosis* is used to indicate the gradual degeneration and death of a cell, but it appears to be somewhat superfluous.

**Causes.**—1. *Loss of Blood Supply.*—When the supply of oxygen and food is cut off, the cells of the part rapidly undergo necrosis. This is well seen in an infarct caused by blockage of a vessel by a blood clot. Even though the cutting-off of the blood is only transient, the cells may be killed. The time necessary varies with the tissue; the secreting cells of the kidney may be killed while the connective tissue survives. Thrombosis of the vessels to a part is followed by necrosis unless a collateral circulation can be quickly established.

2. *Bacterial Toxins.*—The action of toxins is the commonest cause of necrosis. The reader can supply examples for himself. As the toxins act on the vessels of the part and are apt to produce thrombosis, it is evident that the first two causes are often combined. Much depends on the concentration of the toxin; if the toxin is weak inflammation is produced, if strong the result is necrosis.

3. *Physical and Chemical Agents.*—The various physical and chemical irritants which may produce inflammation may also lead to necrosis. Heat is much more injurious than cold. Heat above 45° C. will kill cells, whereas freezing may leave them unaffected. The death of tissue following frostbite is due to injury to the vessels and thrombosis rather than to any direct action on the cells. Electricity, roentgen-rays, and radium rapidly cause cell death if in sufficient concentration. Caustics and other poisons, trauma, and continued pressure may produce the same result.

**Structural Changes.**—Necrosis can be recognized by changes in the cell body and in the nucleus. The *cellular changes* are swelling of the cytoplasm which becomes homogeneous and loses its normal reticulated appearance. There is loss of the normal sharp contour and obliteration of the cell boundaries. Muscle fibers lose their striations and become swollen and homogeneous. *Zenker's degeneration*, which is best seen in the rectus abdominis and diaphragm in typhoid fever, is an example of necrosis with hyaline change. The *nuclear changes* are even more striking, and should be looked for in determining the presence of necrosis. There are three possible changes. (Figs. 14 to 16.) (1) *Chromatolysis* or *karyolysis*, in which the nuclear chromatin appears to be dissolved and the nucleus gradually fades from sight. This is the commonest change. (2) *Karyorrhexis*, in which the nucleus is broken up into a number of small fragments, well seen at the edge of an infarct. (3) *Pyknosis*, in which the nuclear material is con-

densed into a small deeply-staining mass. The student must learn to recognize necrosis under the microscope, because he will encounter tissue death in most diseases and in every organ of the body.

The gross appearance also varies, there being two main types known as coagulation necrosis and liquefaction or colliquative necrosis.



FIG. 14



FIG 15

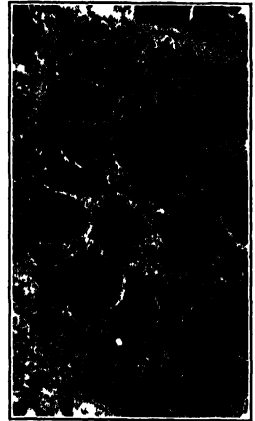


FIG. 16

FIGS. 14 to 16.—Forms of nuclear degeneration in the tubules of the kidney.

FIG. 14. Chromatolysis. The nuclei of the upper tubule have disappeared.

FIG. 15.—Karyorrhexis. The nuclei are broken up into small fragments.

FIG 16.—Pyknosis. The nuclear material is collected into small compact masses.  $\times 500$ .

**Coagulation Necrosis.**—Coagulation necrosis is the common form, and is characteristically seen in infarcts of the kidney or spleen. The part becomes dry, homogeneous, and opaque. There is coagulation of the cytoplasm by intracellular enzymes. Perhaps some of the surrounding lymph may be absorbed and coagulated in the same way. The process is similar to coagulation of the blood. Architectural outlines (glomeruli, tubules) may be preserved though all cellular detail is lost. The coagulated material may remain unchanged for long periods of time, but at the margin of the infarcted area there is a gradual process of absorption owing to the action of proteolytic enzymes in the leucocytes brought by the circulating blood. In course of time calcification may occur.

**Liquefaction Necrosis.**—Liquefaction necrosis occurs in the central nervous system. The necrotic area becomes softened and liquefied, and the fluid material is absorbed leaving a cyst-like space. The change is probably in some way dependent on the high lipid content of the nervous tissue.

**Caseation.**—Caseation is a form of necrosis in which all details of structure are wiped out, with the production of a dry, cheesy, granular material, completely amorphous. In ordinary necrosis, on the other

hand, though the cells are destroyed the stroma is spared, so that the architecture is preserved. Caseation is the characteristic necrotic change of tuberculosis and syphilis. Tuberculous caseous tissue is not chemotactic, so that it attracts no leucocytes; the material therefore remains unchanged owing to the absence of leucocytic ferments. If secondary infection occurs there is invasion of leucocytes and softening may rapidly follow. Caseous material has a high fat content, and calcification is a frequent sequel.

**Autolysis.**—Autolysis plays an important part in producing the picture of necrosis. Take two pieces of fresh tissue, heat one for an hour at 55° C. or boil it for a few minutes, then insert both pieces in the abdominal cavity of an animal. The fate of the two pieces will be very different. The heated piece in which the enzymes have been destroyed will undergo little change, the nuclei staining well after a lapse of months. The unheated piece will pass through the usual changes characteristic of necrosis owing to the autolytic action of its enzymes. If the two pieces are placed in normal saline and incubated, the heated piece will show no change, but the cells of the unheated piece will undergo enormous swelling due to the enzyme breaking down the large molecules into a greater number of small molecules with increase of the osmotic pressure and imbibition of fluid. For this reason dead cells floating in a fluid medium become very swollen. Autolysis proceeds much more quickly outside the body than in necrotic areas such as infarcts, because the plasma contains substances which inhibit the action of the enzymes.

**Fat Necrosis.**—When the pancreatic secretion is liberated in the abdomen owing to inflammation (acute pancreatitis) or injury to the pancreas, the fat-splitting ferment, lipase, acts upon the fat on the surface of the pancreas and in the omentum with the production of small opaque white areas of fat necrosis. The fat is split into glycerin and a fatty acid. The former is absorbed, while the latter remains in the cells as acicular crystals. The necrotic fat cells are easily recognized, because the material which they contain is much less soluble than normal fat, and is therefore not dissolved away in paraffin sections, giving the cells a cloudy appearance. (Fig. 17.) The patches may be rapidly removed; in experimental fat necrosis they have disappeared in eleven days. Calcium may unite with the fatty acid to form a calcium soap, and lime salts may be deposited in the patches of necrosis rendering them permanent. Recent patches are surrounded by a zone of leucocytes. Owing to postmortem changes in the pancreas lipase may be liberated after death and produce fat necrosis. These post-mortem patches can be distinguished from those produced during life as the result of disease by the absence of the zone of leucocytes.

*Traumatic fat necrosis* is quite a different matter. As a result of injury the fat cells of subcutaneous tissue may be injured, and an area of induration partly necrotic, partly inflammatory in character, is produced. The fat cells resemble those in the opaque patches of pancreatic fat necrosis, containing insoluble material in paraffin sec-

tions. A well-marked inflammatory reaction is seen around and within the affected area; foreign body giant cells often form a striking feature so that the lesion may be mistaken for tuberculosis or syphilis. The breast is the most common site.

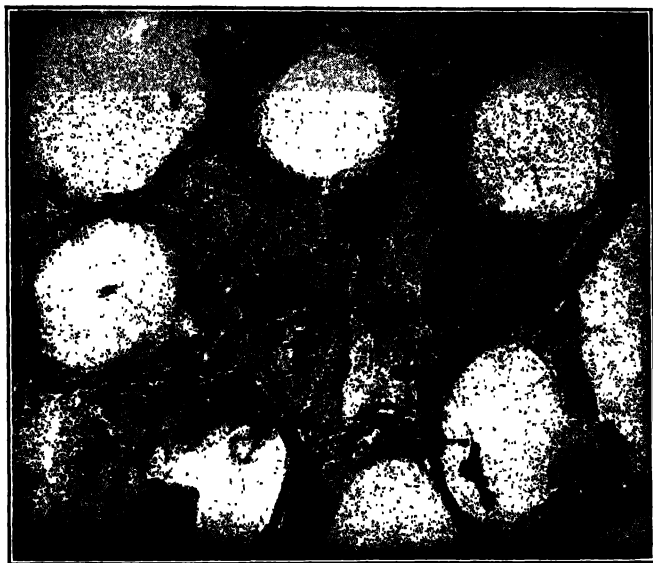


FIG. 17.—Fat necrosis. The necrotic fat cells have a cloudy appearance.  $\times 400$ .

### GANGRENE

Gangrene is death of a part with putrefaction superadded. This definition does not cover so-called dry gangrene, but that condition is not a true gangrene, but rather an ischemic necrosis (infarction) of an exposed part in which simple mummification of the tissues occurs due to evaporation of water. A minor degree of infection by putrefying bacteria may or may not be present.

**Dry Gangrene.**—Dry gangrene is seen in typical form when the arteries to the foot are closed off in old age as the result of arteriosclerosis. The part is cold and pulseless, there is no collateral circulation, and with or without a slight injury gangrene begins in one of the toes, as these are farthest from the blood supply. The part contains so little blood that invading bacteria grow with difficulty in the dead tissue, and the spread of the gangrene is slow. The part becomes dry, shrivelled and dark like the foot of a mummy. Hemolysis of the red blood cells liberates the hemoglobin, which is acted on by the hydrogen disulphide produced by the bacteria with the formation of black sulphide of iron so that the tissues are stained black. The gangrene extends slowly upward until it reaches a point where the circulation is sufficient to keep the part alive. At this level a line of separation

is formed between the living and dead tissue. The line consists of inflammatory granulation tissue, which erodes the dead tissue and finally brings about complete separation. The microscopic picture is one of complete necrosis, but in addition there is usually a blurring and smudging of outline, a disintegration and breaking-up of tissue beyond what is seen in simple necrosis.

**Moist Gangrene.**—Moist gangrene is the same process in a part containing fluid, but the effect on the patient is very different. Gangrene of internal organs (lung, bowel, etc.) is always of the moist variety. It rapidly develops when the venous as well as the arterial flow is blocked and the part becomes filled with blood. This is seen in the limbs (injury to a main artery and vein) as well as in the viscera (strangulated hernia). It may also develop in naturally moist external regions (vulva). Owing to the abundant moisture there is rapid growth of putrefactive bacteria which break down the dead tissue with the formation of foul-smelling nitrogenous end-products such as indol and skatol. The organisms cause liquefaction of the tissues and sometimes gas formation, so that blebs of fluid form under the skin and bubbles of gas give an emphysematous crackling when the part is palpated. Sulphide of iron is formed from the decomposed hemoglobin as in dry gangrene, and the parts are stained dark blue, green, and black. The local spread of the condition is very rapid and there is no attempt to form a line of demarcation. The most serious feature is the great absorption of toxic products which cause profound toxemia and finally death. In dry gangrene little or no absorption takes place.

**Causes.**—The two great factors are loss of blood supply and bacterial infection; often these two are combined. *Senile gangrene* occurs in old people with arteries narrowed by arteriosclerosis, but thrombosis is often responsible for the final occlusion. The gangrene begins in the foot, commonly in the big toe, and is naturally of the dry variety.

*Diabetic gangrene* is very similar in type, though occurring in younger persons. Here again the arteries are narrowed, but in addition the sugar in the tissues favors bacterial growth. *Thromboangiitis obliterans* is often complicated by dry gangrene, usually in the lower limb but occasionally in the upper limb. The spasmodic narrowing of the arterioles in *Raynaud's disease* and in chronic *ergot poisoning* may lead to dry gangrene of the extremities. Sudden occlusion of an artery by *embolism* or *thrombosis* may result in gangrene, but only if the collateral circulation is insufficient for the needs of the part. In a limb with healthy vessels there is no danger of gangrene, but embolism of the superior mesenteric artery is certain to be followed by moist gangrene. *Inflammation* may be complicated by gangrene, especially when the vessels become thrombosed. Gangrene of an inflamed appendix is a good example. *Frostbite* may cause gangrene of such extremities as the fingers, toes, nose and ears. Necrosis is first produced by thrombosis in the vessels, and infection is superadded. Bed-sores are an example of gangrene due to pressure which occludes the vessels leading to necrosis in a previously devitalized part. *Escharotics* (strong acids

and alkalis) kill the tissues by direct action. Acids produce dry gangrene as they coagulate the fluids in the tissues; alkalis produce moist gangrene as they cause liquefaction of the tissue. *Carbolic acid* applications to a finger may be followed by death and gangrene in the course of a few hours.

*Gas gangrene* merits separate consideration. It is one of the most important complications of war wounds, and is occasionally seen after wounds in civil life and following surgical operations. The tissue is killed by trauma or the action of pathogenic bacteria. The dead tissue is then decomposed by saprophytic anaërobic bacilli with the formation of foul-smelling gas and fluid. The chief of these anaerobes are: (1) *Bacillus welchii* (*Bacillus aërogenes capsulatus*), (2) *Vibrio septique* (probably identical with the bacillus of malignant edema), and (3) *Bacillus oedematiens*. The gangrene, which is of the moist variety, affects principally the muscles. Gas can be pressed up and down the fibers, and softening and liquefaction soon follow. Microscopically the sarcolemma is seen to be separated from the fiber by a space filled with toxic fluid, so that the fiber loses its blood supply and quickly dies. As this fluid passes up and down the entire length of the fibers, the spread of the condition is very rapid.

### POSTMORTEM CHANGES

The changes which the body undergoes after death are of great importance. Without a knowledge of these it is possible to make grave errors in performing an autopsy by mistaking the results of these changes for the lesions of disease produced during life. They are also of great importance in medico-legal work in determining how long a body has been dead. The changes unfortunately depend on a number of variable factors, of which the most important are the temperature of the air, the temperature of the body at the time of death, and the presence of widespread bacterial infection. In spite of what one reads in detective stories it is seldom possible to fix the hour of death with any exactness. The two principal changes are rigor mortis and postmortem decomposition.

**Rigor Mortis.**—After death there is a stiffening of the muscles, a condition of rigor. It begins in the muscles of the face and passes downward until the legs are involved. It passes off in the same order. The time of onset as a rule is from one to six hours, and the rigor passes off in from one to two days. These times and the order in which the muscles are involved are of evident importance in medico-legal cases, but the times vary greatly. In persons dying in the midst of severe muscular exertion rigor mortis comes on so quickly that the body may become stiff almost at once. This sudden rigor is seen in soldiers killed in battle and in animals killed during the chase, and is due to the large amount of lactic acid in the muscles. In strychnine poisoning and in tetanus the stiffening is also sudden and very marked. On the other hand it is delayed, slight or absent in wasting diseases,

cachexia, starvation, etc. Rigor mortis is merely a coagulation of the muscle proteins to form myosin or muscle clot, and may be compared with coagulation necrosis. Its subsequent disappearance is due to the softening of the clot by autolytic enzymes. The muscle clot can be broken down by force so that the limb can be freely moved. Once the rigor is destroyed it does not return.

**Postmortem Decomposition.**—Decomposition of the body causes two main changes: (1) discoloration, and (2) softening. *Discoloration* is due to blood pigments and their derivatives. The red blood cells are hemolyzed after death, and the hemoglobin stains the vessel walls and the surrounding tissues. This is most marked in septicemia due to hemolytic bacteria, but in these cases some of the pink staining of the lining of the large vessels may have been antemortem. With the onset of putrefaction sulphuretted hydrogen is formed in the intestinal canal and combines with the iron of the breaking-down hemoglobin to form black sulphide of iron which stains the tissues green and black. The color is first seen in the skin of the abdominal wall and on the surface of the abdominal organs.

*Postmortem softening* is due to the action of ferments, partly autolytic ferments in the tissues, partly the proteolytic ferments of the saprophytic bacteria causing putrefaction. The process is similar to that which occurs in moist gangrene. As the result of this ferment action the tissues are first softened and finally liquefied. This *postmortem digestion* may thin the stomach wall and cause actual perforation, so that the stomach contents are found in the abdominal cavity. The hole in the stomach wall must not be mistaken for an antemortem lesion, traumatic or otherwise. The distinction is made by microscopic examination of the edge of the opening; in the postmortem lesion there is no inflammatory reaction. Softening of the pancreas may also occur, and the pancreatic juice may escape and produce areas of fat necrosis, but these also show no leucocytic reaction. The change proceeds very rapidly in hot weather, and when death has been due to some septicemic condition invasion of the body by putrefactive bacteria may occur even before death. When bacteria are found in the tissues at autopsy it must be realized that this may be merely a terminal invasion with no causal relation to the disease from which the patient died. Gas may be formed by the anaërobic saprophytes as in gas



FIG. 18.—Foamy liver. Gross specimen showing the vacuolated appearance.

gangrene, and the liver may be full of bubbles like a sponge, a condition known as *foamy liver*. (Fig. 18.) When a body is kept in cold storage autolysis and bacterial growth are greatly delayed, and when it is injected with chemical poisons as in the process of embalming, both ferments and bacteria are destroyed, and the tissues are preserved for long periods. In the kidney of an embalmed body which had been buried for nine months I found that the red blood cells stained perfectly and showed no evidence of hemolysis. The fixation of tissues for microscopic examination depends on the same principle of destroying autolytic ferments and bacteria as quickly as possible.

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## CHAPTER III

### CIRCULATORY DISTURBANCES

THE circulation of the blood through a part may be interfered with in a number of ways, each of which adversely affects the particular tissue supplied: (1) There may be too much blood in a part or too little; (2) the vessel wall may be broken and the blood escape; (3) the blood may clot in the vessel and the clot may be detached and carried by the circulation so as to lodge in another vessel; (4) the fluid part of the blood may escape through the intact vessel wall and collect in the tissues. We have therefore to study: (1) hyperemia and ischemia, (2) hemorrhage, (3) thrombosis and embolism, and (4) edema. Hyperemia and congestion have the same meaning, but in practice the term hyperemia is usually applied to the active dilatation of arterioles and capillaries, as a result of which too much blood goes into the part, while congestion is applied to the passive dilatation of veins caused by some obstruction to the circulation, as a result of which too little blood gets out of the part.

#### ARTERIAL AND CAPILLARY HYPEREMIA

Active hyperemia is a dilatation of the arterioles and capillaries, which may be dilated together or singly. It may be regarded as a physiological response to a call of the tissue for more blood. It must be realized that the capillary bed of an organ at rest is never all in operation at one time. In a healthy kidney only a limited number of glomeruli are working at any given moment, and it is only through the capillaries of these glomeruli that an active circulation is going on. The remainder remain collapsed. Whenever there is a call for more work the latent capillary bed becomes opened up. The same difference is observed between a muscle which has been actively contracting and one which is at rest. The active organ shows an active hyperemia. Under normal conditions the whole of an organ does not function at the same time. Thus one part of a secretory gland works while another part rests and recovers. This is true even of muscles, for in moderate activity only a moderate number of fibers contract fully while the others rest, but in extreme activity all the fibers are called into play. This is the basis of the idea of "reserve force." An organ is always larger than is necessary for normal needs. It is only when an extraordinary call is made upon it that it exerts itself to the full, *i. e.*, all the cells work at the same time. The application of this conception to circulatory arrangements is of extreme importance, for it throws light on many obscure problems of pathogenesis. It has always been

difficult to understand why in an organ of uniform structure, such as the liver, a blood-borne toxin tends to produce focal rather than diffuse lesions. The explanation appears to depend on the fact that some parts of the organ are relatively ischemic and therefore protected for a time from the injurious agent, while others are flooded with blood

and thus exposed to damage. (Fig. 19.) For the same reason pyogenic bacteria circulating in the blood will set up localized abscesses in the kidney rather than a diffuse inflammation.

Great active hyperemia of arterioles and capillaries is seen in inflammation. A comparison between the capillary bed in a normal and an inflamed omentum will soon prove the truth of this statement. In the early stages of pneumonia the vessels in the walls of the alveoli show an extreme degree of hyperemia. Inflammatory hyperemia is due to the direct action of toxins on the walls of the vessels, because it occurs when all the nerves to the part are cut, and yet nervous influence does exert some influence upon it. Active hyperemia may largely disappear after death. Temporary anemia caused by pressure on a vessel is followed by active hyperemia when the pressure is released, due probably to damage to the vessel walls from the lack of



FIG. 19.—The upper glomerulus is full of blood and active; the lower one is ischemic and resting.  $\times 200$ .

oxygen. This must be borne in mind when performing a bloodless operation with the aid of a tourniquet; if the smallest vessels are not tied there may be troublesome bleeding later when the hyperemia has had time to become established.

The work of Krogh has shown that the capillaries possess a power of contraction and dilatation independent of that of the arterioles, although usually the two sets of vessels behave alike. Histamine causes contraction of the arterioles but dilatation of the capillaries, and a weak solution of adrenalin behaves in the same way. The temperature of the skin depends on the rate of flow of the blood through it, and this in turn depends on the degree of dilatation of the arterioles. The color of the skin, on the other hand, depends on the dilatation of the capillaries. Thus the skin may be hot and pale

(dilated arterioles and contracted capillaries), hot and red (dilated arterioles and dilated capillaries), or cold and purple (contracted arterioles and dilated capillaries). These variations are of importance in the study of the vasomotor disorders. In the operation of lumbar sympathectomy undertaken to relieve vasomotor disturbances in the legs the arterioles dilate and the legs become warm when the vaso-constrictor nerves are cut, but the capillaries still remain undilated.

### VENOUS CONGESTION

Venous congestion or passive hyperemia is a condition in which the blood accumulates on the venous side of the vascular tree. The congestion may be general or local. Both of these may be acute or chronic. Of these various forms chronic general venous congestion is by far the most important.

**General Venous Congestion.—Causes.**—As the condition is general the cause must be central. There are only two organs through which all the blood in the body must pass. These are the heart and the lungs. Obstruction to the circulation through either of these organs will give rise to general venous congestions. As the obstruction is usually chronic in type the congestion will be chronic. In the *heart* the common cause is mitral stenosis, but mitral incompetence and aortic valvular disease will lead in the end to the same result. Chronic myocardial failure from whatever cause is also associated with chronic venous congestion. The means by which the congestion is produced is rather different in these different cases. In mitral stenosis there is constant obstruction to the flow of blood through the mitral valve, so that blood collects in the lungs, in the right side of the heart, and finally in the veins which become distended to accommodate the increased amount. In aortic valvular disease and in myocardial failure not enough blood is pumped into the aorta, so that the blood-pressure tends to fall. In order to compensate for this there is a tonic contraction of the arterioles so that the volume of the arterial system is diminished and blood is squeezed into the venous system, where it tends to accumulate.

In the *lungs* the chief causes of obstruction are emphysema and fibrosis. In emphysema there is great distention of the alveoli with destruction of the alveolar walls and narrowing of the capillaries in those which remain. The result is a marked obstruction to the pulmonary circulation with distention of the right side of the heart and accumulation of blood in the veins. Fibrosis of the lungs as the result of tuberculosis or other chronic infections also leads to obliteration of the pulmonary capillaries with resulting venous congestion.

These forms of congestion are of the chronic type. If cardiac failure is more acute, usually left ventricular in type, the venous congestion will also be acute. This type of failure often develops as a terminal phenomenon, and as the lungs are the first to suffer, it is seldom that autopsy fails to reveal some degree of pulmonary congestion.

**Effects of Chronic Venous Congestion.**—These are both general and local. The *general effects* are due to insufficient oxygenation. Owing to accumulation of blood in the dilated veins the speed of the circulation is slowed down and the blood is not sufficiently aerated in the lungs. Moreover the edema of the lungs which so commonly develops still further prevents a proper interchange of gases. Owing to the resulting anoxemia there will be a varying degree of *dyspnea* or shortness of breath. As the blood remains unduly long in the venules and capillaries, there is a marked increase in the amount of reduced hemoglobin, the blood becomes more venous in type, and the patient manifests *cyanosis*, a blueness or lividity of the skin and mucous membranes, well seen in the ears and lips. Cyanosis is seen in other conditions in which the blood is imperfectly oxygenated, especially in pulmonary disease and in congenital heart disease where an abnormal communication exists between the right and left sides of the heart. Owing to the general congestion the walls of the veins are injured and fluid escapes from the vessels into the tissues causing *edema*, especially in dependent parts such as the feet. Fluid may also pass into the serous cavities with the production of ascites, pleural effusion, etc.

The *local effects* are observed in the individual organs. The condition of the *lung* depends on the site of the obstruction. If the obstruction is in the lung itself there will be no congestion there, but, if, as is usually the case, it is in the heart, the lung will show marked changes. In mitral stenosis the lung is commonly dark brown in color and of tough consistence, a condition known as *brown induration*. Microscopically the vessels in the alveolar walls are dilated, varicose, and in section may give the wall a beaded appearance. The walls themselves are thickened. But the most characteristic finding is the presence in the alveoli of large phagocytic cells filled with yellow blood pigment which gives the reaction for iron. (Fig. 20.) These cells are known as "heart failure cells," but their presence does not necessarily indicate that the heart is failing—merely that there is some central obstruction. The pigment is derived from the red blood cells often seen lying within the alveoli and due to hemorrhage from the distended vessels. There has been a vast amount of controversy regarding the origin of these phagocytes, some maintaining that they are the desquamated epithelial cells which line the alveoli, others that they are histiocytes (reticulo-endothelial cells) contained in the alveolar septa. The latter view is probably the correct one. The pigment is carried by the phagocytes into the lymphatics and is distributed throughout the framework of the lung, where it excites a certain amount of fibrosis. The pigment is therefore responsible for the "brown induration." As the result of alveolar hemorrhages blood may appear in the sputum; indeed mitral stenosis is the second commonest cause of hemoptysis. The blood in the alveoli is partly converted into bilirubin, and the bilirubin content of the blood plasma may be distinctly above normal, so that mitral stenosis is one of the conditions which may give rise to a latent jaundice. Shortly before

death a certain amount of *hypostatic congestion* usually occurs, owing to loss of the vascular tone. It is most marked in the dependent

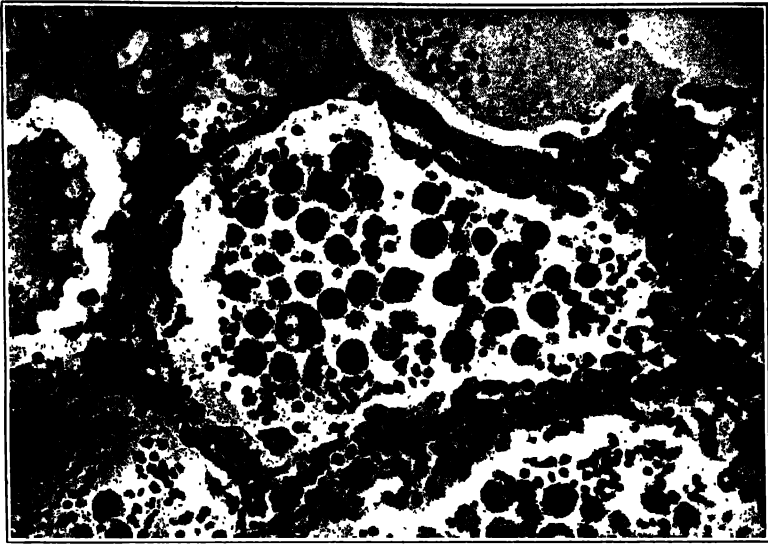


FIG. 20.—Heart failure cells in the lung. The alveolar walls are greatly thickened.  $\times 250$ .

parts of the lung, and may be accompanied by transudation of fluid into the alveoli. The condition, which is best seen in patients who have had to lie on their backs for some time, closely resembles the postmortem hypostasis which occurs in the dependent parts of the lung after death.

The *liver* is early involved owing to its anatomical position. When the heart is failing the liver is often enlarged and tender, both of which features may disappear under treatment with rest and digitalis. In long-standing cases the liver may become shrunken and very firm, a condition of *cyanotic induration*. But the characteristic picture in chronic venous congestion is the *nutmeg* liver, the cut surface showing

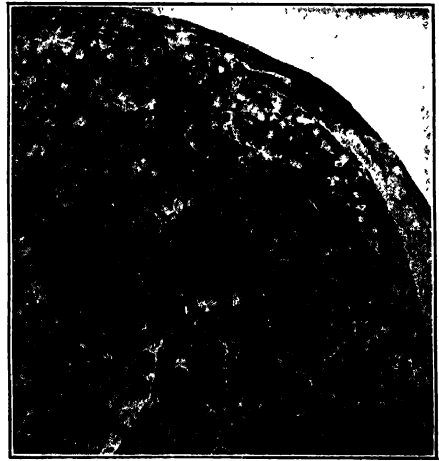


FIG. 21.—Nutmeg liver. The cut surface has a mottled appearance.

a mottled appearance of dark brown and light yellow areas. (Fig. 21.) The dark areas represent the congested center of each lobule, the light

areas are the fatty peripheral part. Microscopically, the sinusoids at the center of the lobule are distended with blood, and the liver cells are degenerated and atrophic, probably mainly as the result of oxygen deficiency (anoxia). At the periphery of the lobule the congestion is slight and the liver cells comparatively normal, though they often show a considerable amount of fatty degeneration. In very chronic cases there may be a good deal of collapse of the lobules, so that the fibrous tissue round the portal tracts may seem to be increased. The end-result may not be unlike that of cirrhosis of the liver; owing to the destruction of liver cells, islands of regeneration are formed which give the organ a slightly nodular appearance.

The *spleen* is enlarged and firm, but the enlargement can seldom be detected clinically. The splenic pulp is filled with red cells, and the lymphoid tissue is atrophic.

The *kidneys* are slightly enlarged, firm, and dark red. The capillaries in the glomeruli and the intertubular vessels are intensely congested. The capsular space and the tubules may contain red blood cells and albumin. The urine often shows albuminuria and casts, and the renal function as shown by the dye excretion test is markedly impaired. With treatment of the heart condition the renal function is recovered.

**Local Venous Congestion.**—When the main vein from a region or an organ is obstructed a condition of local venous congestion is produced. The obstruction may be acute or chronic. *Acute obstruction* is usually due to thrombosis in the vein, but may also be caused by sudden pressure on the vein as in strangulation of a loop of bowel, twisting of the pedicle of an ovarian cyst, etc. The result is very similar to the production of a hemorrhagic infarct which will be described presently. There is no time for a collateral circulation to be set up, so that there is intense engorgement of the venules and capillaries; many of these rupture, and there is hemorrhage into the part which becomes of a dark purple color. Under the microscope the tissues are seen to be stuffed with blood. The condition is best observed in strangulation of the bowel, but may also occasionally be observed in the spleen, kidney, and other organs.

In *chronic obstruction* due to the pressure of tumors, enlarged glands, aneurism, etc., a collateral circulation is gradually established, so that the results are less severe. If the veins of the collateral circulation are superficial they can readily be seen and offer useful help in making a correct diagnosis. Even when they cannot be seen with the unaided eye, they can be made visible by photographing the area using infra-red films. In obstruction of the superior vena cava these distended superficial veins are seen coursing over the clavicle and the upper part of the chest, while in the case of the inferior vena cava they pass upward on the abdominal wall. An important form of chronic local venous congestion is that due to obstruction of the portal vein, usually the result of cirrhosis of the liver. In *portal obstruction* the radicles of the portal vein become distended and varicose. Important varicosities are formed at the lower end of the esophagus and the lower end

of the rectum. The latter form hemorrhoids or piles, and the former may rupture causing hemorrhage into the stomach which may prove fatal. Just as coughing of blood (hemoptysis) is a sign of pulmonary congestion, so vomiting of blood (hematemesis) is a sign of portal congestion. Fluid may pass from the branches of the portal vein into the peritoneal cavity causing ascites.

### ISCHEMIA

Ischemia is a local anemia, a cutting-off of the arterial blood supply to a part. It may be sudden or gradual. *Sudden obstruction* is, of course, produced when a vessel is ligatured, but in disease the usual causes are thrombosis and embolism. The result depends on the question of collateral circulation. If this can be established rapidly and adequately, blood reaches the part by other channels, and no serious damage is done. If such a circulation cannot be established, part of the whole of the area affected will quickly die. This change, which is well seen in the heart, spleen, kidney, and brain, is called infarction and will be studied in connection with the process of embolism.

*Gradual obstruction* is usually due to arteriosclerosis in which thickening of the intima leads to narrowing of the lumen. The area supplied atrophies, the parenchymatous tissue undergoes necrosis, disappears, and is replaced by fibrous tissue. This change is well seen in the kidney and the myocardium (ischemic necrosis). In the brain it leads to softening. Gradual obstruction of the arteries may also be produced by pressure from without, but this is of little importance apart from the pressure of splints and the formation of bed-sores. Ischemia may be caused by prolonged arterial spasm in ergot poisoning and in Raynaud's disease, in both of which conditions gangrene of the extremities may develop.

### HEMORRHAGE

Hemorrhage or the escape of blood from a vessel may occur from a variety of causes, some of which are simple, while others are obscure and indeed unknown. The hemorrhage may be due to a break in the wall of the vessel either from trauma or disease. In other cases there seems to be no distinct rupture of the wall, the red cells escaping out by a process of diapedesis. It is probable that many tiny hemorrhages occur in this way. The smallest hemorrhages, often no larger than a pin's head in size, are called *petechiæ*, while larger extravasations are called *ecchymoses*. When a hemorrhage of some size occurs into the tissue it may form a tumor-like swelling known as a *hematoma*.

Spontaneous massive hemorrhage is due to rupture of a vessel. The rupture may be caused by a patch of atheroma (arteriosclerosis) which weakens the vessel wall; a good example of this is cerebral hemorrhage. Local dilatation of the lumen with thinning of the wall (aneurism formation) will produce the same result. A second class of

case is the septicemias, in which petechial hemorrhages, particularly in the serous membranes, are of frequent occurrence. Here the probable cause is injury of the capillary endothelium by the bacterial toxins, although this is difficult to prove. In some instances (bacterial endocarditis, typhoid fever) clumps of bacteria may lodge in the capillaries and cause hemorrhage. A third group is that of the bleeding diseases which will be discussed in the chapter on the Blood. Some of the chief of these are pernicious anemia, leucemia, and purpura. In the last-named there is a great decrease in the number of blood platelets, but in none of them can it be said that we really know the cause of the hemorrhage.

**Changes in the Extravasated Blood.**—When the hemorrhage is very small, *i. e.*, petechial in type, the red cells may be removed by phagocytes. When it is of any considerable size the red cells are broken down so that hemoglobin is liberated, and this stains the surrounding tissues. The coloring matter of the hemoglobin is disintegrated into two moieties; one is iron-free and called *hematoidin*, the other contains iron and is therefore called *hemosiderin*. The hematoidin may be deposited in the form of granules or rhombic crystals which are seen around old cerebral hemorrhages, but some of it is converted into bilirubin which is soluble and therefore carried away and excreted in the bile. Large hemorrhages such as that of a ruptured tubal pregnancy may therefore be accompanied by jaundice. The hemosiderin is taken up by phagocytic cells, and these give the Prussian blue reaction for iron.

**The Arrest of Hemorrhage.**—This can best be studied in a vessel which has been divided. There is first temporary arrest of the hemorrhage by the formation of a blood clot, followed by permanent arrest due to the formation of an inflammatory exudate which becomes organized and seals the vessel.

The *temporary clot* is produced by the coagulation of the blood, a process which will be considered in connection with thrombosis. The temporary clot is of two varieties, the red and the white. The *red clot* is composed of fibrin containing red cells in its meshes. The *white clot*, which is a thrombus, consists almost entirely of platelets, which form a sticky mass that adheres to the cut edges and serves to plug the hole in the vessel wall. The temporary clot is like a nail, the head of which is formed by the white clot and closes the cut end of the vessel, while the stem is formed by the red clot which extends along the vessel for some distance.

The *permanent clot* results from the organization of the temporary clot. As the result of the injury an inflammatory exudate is formed around the latter, new capillaries and fibroblasts grow in, the clot is vascularized and fibrosed, and the opening in the vessel is finally plugged by a mass of fibrous tissue firmly adherent to the edges of the hole. The arrangement just outlined is a singularly beautiful one, whereby the blood remains fluid in the vessels so that it can traverse the finest capillaries, yet the moment it is shed it clots and plugs the



hole in the vessel wall. It is like a fire-sprinkler system, unnoticed as long as all goes well, but ready for any emergency at a moment's notice.

This process of healing only occurs properly in the absence of infection. If sepsis is present the formation of the permanent clot is interfered with, the temporary clot may be softened by the bacterial ferments, and *secondary hemorrhage* may occur one or two weeks after an operation. Before the days of asepsis such an accident was a common occurrence.

### THROMBOSIS

Thrombosis is the formation of a solid body, the thrombus, from the elements of the streaming blood. All the elements, platelets, fibrin, red cells, and leucocytes, may enter into the formation of a thrombus, but the first two are the most important. Thrombosis is quite different from clotting, although clotting may take part in the formation of a thrombus. The normal clotting of blood will first be described.

**The Clotting of Blood.**—When blood is shed and comes in contact with injured cells it forms a solid clot composed of a network of fibrin threads. Clotting can occur within the vessels when the blood is in a state of stasis. Clotting has been compared to the sudden freezing over of a pond, whereas thrombosis is like the formation of a snow-drift with snowflakes represented by platelets. The process is complex and imperfectly understood, but Howell's views are the most favored at present. The fibrinogen in the plasma is acted on by a ferment named thrombin to form fibrin. The thrombin in turn is formed by the interaction of prothrombin with calcium salts. The prothrombin is prevented from uniting with the calcium under normal conditions by the presence of antithrombin. The balance between prothrombin and antithrombin is delicate and easily upset, and the antithrombin is neutralized by thromboplastin or thrombokinase which is liberated as the result of cellular injury. The injured cells may be tissue cells, or platelets. When the antithrombin is eliminated, the whole complex machinery of clotting is set in motion. Injury is the key to the process. If this can be prevented coagulation will not occur. Removal of the calcium by the addition of oxalate or citrate has a similar effect. The clotting mechanism appears to be subject to neurogenic influence (de Takáts). Adrenergic stimuli increase whilst cholinergic stimuli decrease the tendency to clotting. Fear, apprehension, nervous strain and hemorrhage increase this tendency.

*Vitamin K* (Koagulationsvitamin), as its name implies, is essential to proper coagulation, because it is necessary for the formation of prothrombin. In animals fed on a diet deficient in vitamin K, the blood prothrombin falls and a tendency to hemorrhage develops. In man the deficiency of the vitamin is more likely to be due to lack of absorption than to inadequate supply. As bile is necessary for absorption of the vitamin from the bowel, low prothrombin and a marked tendency to bleeding is characteristic of obstructive jaundice. Hemor-

rhage in the new-born, especially intracranial hemorrhage, is due to lack of vitamin K, as the vitamin is largely produced by intestinal bacteria, which are absent during the first few days of life.

After death the blood clots in the heart, arteries, and veins but not in the capillaries. When blood clots in the larger vessels all the elements are involved, and the clot is soft and red, the "currant-jelly" clot. This type of clot is also seen in the heart when clotting is fairly rapid. But if it is slow the red cells fall to the bottom, and the clot consists only of leucocytes and fibrin. Such a clot is firmer and pale yellow in color, and is known as a "chicken fat" clot. The lower part of the clot is often red and the upper part pale. Microscopically the clot has a characteristically homogeneous appearance. At first the individual red cells can be distinguished, but soon they become fused into a uniform structureless mass. The clot shows none of the delicate architecture of a thrombus.

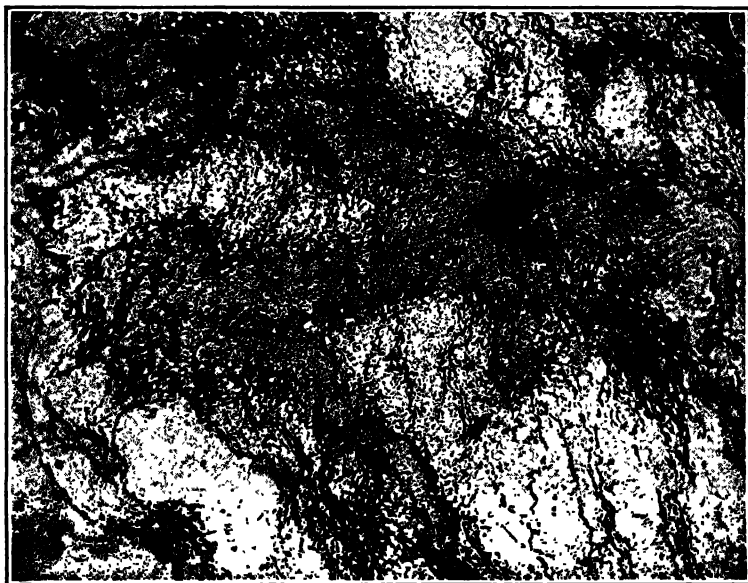


FIG. 22.—Antemortem thrombus, showing laminæ of platelets outlined by fibrin and connected by fibrin threads. Fibrin stain.  $\times 100$ .

**Mechanism of Thrombosis.**—Thrombosis is an active and vital process compared with clotting. A clot is composed mainly of fibrin, whereas the chief element in a thrombus is the platelets, although fibrin is an important constituent of some thrombi. For a thrombus to be formed the blood must be in motion. In a stained smear the platelets appear as small nuclear bodies arranged in clumps, but moving pictures of streaming blood show that this nucleus is a very small part of the platelet, and that it is surrounded for a distance of 3 or 4 nuclear diameters by a thin veil-like cytoplasm which is

actively ameboid and throws out pseudopodia that are arrested by any irregularity of surface. The platelets readily become agglutinated and adhere to the site of thrombus formation, more and more falling out of the blood stream as it passes by. They form ridges running at right angles to the stream. When they adhere to the surface they liberate thromboplastin, and this sets in motion the machinery of fibrin formation, so that festoons of fibrin threads hang between the ridges and entangle many red blood cells and leucocytes. (Fig. 22.) A thrombus is thus composed of platelets and fibrin, with a varying

admixture of red cells and leucocytes. (Fig. 23.) The proportions vary greatly as will be seen presently. The thrombus at first forms a red mass, on the cut surface



FIG. 23. — Antemortem thrombus. Numerous cells between the strands of platelets.  $\times 75$ .



FIG. 24. — Thrombus showing lines of Zahn.

of which the sheets of platelets are seen as interlacing white lines. They project slightly above the free surface forming corrugations known as the *lines of Zahn*. (Fig. 24.) In time the various elements are fused together to form a hyaline mass. The platelets present this hyaline appearance from the beginning. The formation of a platelet or white clot is a more fundamental and primitive process than the formation of a fibrin or red clot, for it is seen in response to vascular injury throughout the animal kingdom, while fibrin formation is only met with in the higher vertebrates.

In pathological lesions in man the two forms are often combined.

Platelets are deposited on an injured vascular surface and a white clot is built up until the vessel is nearly occluded. The blood stream is slowed, and fibrin is deposited in large amount on the surface of the thrombus, until the lumen is completely closed. The blood in the vessel, usually a vein, then clots in the usual way, and the red clot may extend up to the point where the vessel comes off from the parent trunk. The red clot projects into the moving blood stream, again platelets are laid down and a white clot is formed, and in this way the thrombus may extend up a series of veins for a long distance, involving vessels of ever-increasing size.

The process of thrombosis can be directly observed microscopically through the transparent wall of a celloidin tube connecting the carotid artery with the jugular vein. This method was introduced by Rowntree and Shionoya, and has been used with great effect by Best in experiments on the effect of heparin in inhibiting thrombus formation. In these observations one is struck by the speed with which a thrombus is formed, often only a matter of a few minutes.

*Heparin* was first obtained from the liver by Howell in 1916, hence its name. It appears to be produced by the mast cells of Ehrlich, the metachromatic granules of which are stained by toluidin blue in a manner similar to heparin. Best has shown that heparin acts as an antithrombase preventing the agglutination of platelets to form white thrombi, and interfering with the union of prothrombin and calcium to form thrombin. Heparin has proved of great value in bloodvessel surgery, permitting end-to-end anastomosis, suture of vessels, etc., without subsequent thrombosis.

Cattle suffer from a hemorrhagic disease caused by eating decayed sweet clover. The hemorrhagic agent has been isolated from the clover and finally synthesized. It is 3,3'-methylene-bis-(4-hydroxycoumarin), known more briefly as *dicumarol*. It resembles heparin, in prolonging the coagulation time, and it has the advantage that the action is much more prolonged and that it can be taken by mouth instead of being injected intravenously.

**Causes.**—Thrombosis is the result of an upset in a delicate balance. Several things may cause this upset, some of which are known, some unknown. Three factors which are known to play a part are: (1) injury to the intima, (2) slowing of the blood stream, (3) change in the chemical composition in the blood.

*Intimal injury* may be traumatic or inflammatory. *Traumatic injury* is best studied in operation wounds. When an artery is ligatured the inner coat is torn, and platelets are at once deposited on the injured area. Until the advent of heparin thrombosis was the great problem of the surgeon anastomosing arteries or suturing vessels. A rough spot on the intimal surface may be the starting point of a thrombus, as in atheromatous ulcer of the aorta. Martland emphasizes the frequency with which injury by a blunt object, as in automobile accidents, is responsible for thrombosis in the veins of the leg. *Inflammation* of the vessel wall is a common cause of thrombosis, particularly

in the veins, where the condition is called thrombophlebitis. When the heart valves are inflamed, platelet thrombi are deposited on their surface to form "vegetations." The presence of inflammatory cells in the wall of a vessel at the site of a thrombus does not prove that inflammation has been the cause of the thrombosis, for it can be shown experimentally that the presence of a thrombus may excite an inflammatory reaction in the vessel wall with which it is in contact. In the past too much emphasis has been laid on the necessity of a preceding inflammation. Thus Welch's dictum that nearly every case of venous thrombosis is preceded by infection can no longer be accepted.

*Slowing of the blood stream* is of particular importance in thrombosis of the veins, particularly those of the legs. This factor is discussed below in connection with thrombus formation in those vessels.

The *blood platelets* may undergo changes which predispose to thrombosis. After childbirth and severe surgical operations, conditions often followed by the formation of thrombi in the veins, there is a pronounced rise in the number of platelets and an increase in their agglutinability or stickiness. Both of these changes appear about the fourth day and reach their peak about the tenth day, the very period during which thrombosis with its attendant threat of embolism is likely to be observed clinically.

*Chemical changes in the blood* constitute the unknown factor. It is safe to say that such changes must play an important part in many cases, but at present there is no precise information available. If an excess of *heparin* inhibits thrombosis, a deficient supply must favor it. A sufficient supply of *vitamin K*, produced in the liver, is necessary for blood coagulation, and an excess might stimulate the process unduly. Doubtless other factors, still unknown, play their part. It has been observed that *weather conditions* are related to thrombosis. It is commoner in hot and cold spells, and is less likely to occur in regions with a uniform climate. The action may be through the skin on the vegetative nervous system, slowing the circulation and thus favoring thrombosis.

Perhaps the commonest factor favoring thrombosis in the veins of the leg is the sudden confinement to bed of a person who has previously been moving around actively.

**Varieties and Sites.**—Thrombi are divided into pale, red, and mixed. The *pale thrombus* is in a sense a pure thrombus, composed almost entirely of blood platelets. It is seen to advantage in the "vegetations" which form on the valves of the heart in acute endocarditis. The greater part of such a vegetation is composed of a fused mass of platelets which have been deposited on the inflamed surface of the valve from the blood as it passes over it. A *red thrombus* is composed largely of fibrin and red blood cells entangled in it, although there is always a basis of platelets. Such a thrombus, which is likely to be formed when the process of thrombosis is rapid, is more soft and friable, and it is evident that it may easily be confused with a mere clot formed postmortem by clotting of the blood. Naked eye or if

required microscopic examination of the site of attachment of the thrombus may be necessary. A true thrombus is adherent to the underlying tissue and when detached a raw surface is left. A post-mortem clot has no attachment. A *mixed thrombus* is partly pale and partly red, *i. e.*, partly platelet and partly fibrinous in composition. Most thrombi are of this type. A thrombus may be *septic* or *aseptic*, depending on whether it is infected with pyogenic microorganisms. The difference is chiefly of importance in connection with the effect which may be produced if the thrombus is carried by the blood to some other organ, and will be discussed in relation to embolism.



FIG. 25.—Pale thrombi adherent to auricle and auricular appendix.

Thrombi may also be divided according as they arise in the heart, arteries, veins, and capillaries. Each of these presents special features of its own.

*Heart.*—Here it is necessary to distinguish between true thrombi and the postmortem clots which are so constantly found in the chambers of the heart. These clots may be of the “currant-jelly” type (soft and red) or the “chicken fat” type (firm and yellow), depending on the rapidity with which they are formed. The commonest type of true thrombus is the *agonal* thrombus which rapidly forms shortly before death. Such a thrombus is usually seen on the right side, where it forms a yellow stringy mass attached to the apex of the ventricle and often passing through the pulmonary valve. It is composed chiefly of fibrin, and is characteristically seen in lobar pneumonia. Thrombus formation in the auricle and its appendix is common in

heart failure. (Fig. 25.) A *ball thrombus* forms a globular mass occasionally seen in the auricular appendix in mitral stenosis. Globular thrombi may be attached to the heart wall by a pedicle, and for centuries these were described and figured in medical books as “cardiac polypi,” a kind of tumor of the heart. A thrombus is constantly found over the necrotic patch of heart muscle which results from sudden occlusion of the coronary artery, provided that there is involvement of the endocardium. The vegetations of endocarditis have already been described; they may occur on the mural endocardium as well as on the valves.

*Arteries.*—Thrombosis occurs much less commonly in arteries than in veins. For one thing, the rapidity of the blood stream is less favorable. In localized dilatations (aneurisms) there is a backwater in the stream and thrombus formation is common, especially in aortic aneurism. The clot is laid down in successive layers and presents a characteristic laminated appearance. A thrombus may be formed on an atheromatous ulcer of the aorta, but much less frequently than might be expected.

*Veins.*—The veins are the commonest site of thrombosis. Such thrombosis may be divided into two groups: (1) thrombophlebitis and (2) venous thrombosis. *Thrombophlebitis* is the result of inflammation of the vein wall (phlebitis), *e. g.*, cavernous sinus thrombosis in infection of the face and thrombosis of the pelvic veins in puerperal sepsis. The changes in the vascular endothelium usually cause the clot to be firmly attached to the vessel wall, so that there is little danger of its becoming detached. If the infection is septic the thrombus tends to become softened and disintegrate. *Venous thrombosis*, much the more common type, is seen particularly in the veins of the leg following operations, in congestive heart failure, and as the result of trauma (automobile accidents, etc.) The vein wall usually shows no evidence of inflammation. Even if inflammatory cells are observed in the wall, these may be secondary to irritation caused by the thrombus, as already pointed out, rather than an indication of a primary phlebitis. The earliest thrombus, consisting essentially of platelets, represents the so-called white head, but on this is soon superimposed a mass of erythrocytes, forming the soft red tail which waves free in the blood stream. It is the friable tail that tends to become broken off and form a moving body which may cause fatal pulmonary embolism (see below), or the entire loosely attached thrombus may share this fate. A thrombus in a vein may form in a valve pocket. In this case it will present a V-shaped gap caused by the valve commissure. This, together with the lines of Zahn, provides the best gross evidence of antemortem formation.

The venous thrombosis which follows surgical operations and delivery occurs for the most part between the fourth and the tenth day. Not only are the platelets increased in number during this period, but there is a marked augmentation of their normal stickiness, due probably to the fact that large numbers of young platelets are produced (Wright). This increase in stickiness and in numbers may well be an important factor in the production of postoperative and puerperal thrombosis.

Since the days of Virchow it has been believed that the common venous thrombi originated in the femoral vein and its valve-pockets, and a red "coagulation thrombus" was supposed to form in the stagnant mass of blood in the veins distal to the obstruction. More recent observations have shown that there are four venous areas in the leg in which thrombosis may commence: (1) plantar veins, (2) veins of the calf muscles, (3) veins of the adductor muscles, and (4) the visceral pelvic veins, especially in obstetrical patients. It is probable that a

coagulation thrombus is first formed in areas where the stream is sluggish, that the process extends in the direction of the bloodflow, and that when a large vein (femoral) is reached in which the stream is rapid, platelets are deposited with the formation of a white thrombus. It is the youngest part of the clot which is likely to be detached and form an embolus.

Frykholm suggests that the venous thrombosis which occurs in the leg after operation or when a previously active person is confined to bed is due to intimal injury caused by collapse of the veins, as the walls are no longer separated by a long column of blood. Intima is pressed against intima, more especially in regions exposed to external pressure when the patient is in bed. As the nourishment of the endothelial cells depends on the blood with which they come in contact, there is reason to believe that these cells may be injured by the continued pressure and may liberate thromboplastic substances which induce coagulation in the minimal stream of blood that percolates through the crack-like lumen. From this small beginning the process extends upwards. In support of this idea may be mentioned the fact that venous thrombosis has occurred in elderly patients who have spent long winter nights sitting in deck chairs in air-raid shelters; pressure on the back of the thighs has been followed by venous thrombosis and in some instances by fatal pulmonary embolism.

*Capillaries.*—In inflammatory conditions the capillaries often contain capillary thrombi; these are hyaline and structureless, and appear to be formed by the fusion of red blood corpuscles. These masses are therefore not true thrombi. It is worth noting that postmortem clots are never seen in the capillaries; some hours after death the blood in the capillaries loses the power of clotting.

*Clinical Effects.*—These depend on the organ and on the collateral circulation. When one of the main veins of the leg becomes thrombosed the vessel is tender and feels like a hard cord. Edema often develops, and the leg may be swollen from the foot to the thigh. Simple venous obstruction such as that produced by ligature of the femoral vein does not cause edema. Lymphatic obstruction is probably the deciding factor, and this is often present owing to spread of the infection from the vein to the lymphatics. Thrombosis of the portal vein is followed by a rapid accumulation of fluid in the abdominal cavity (ascites). Thrombosis of the superior mesenteric vein will produce the picture of hemorrhagic infarction with diffuse hemorrhage in the tissues. The same is true of the lung, and more rarely of the spleen and kidney. Thrombosis of the coronary arteries is followed by rapid necrosis of the area of myocardium involved, accompanied by severe cardiac pain and often followed by death. Thrombosis of the cerebral arteries causes softening of the brain. Finally the thrombus or a portion of it may become detached from the vein in which it is formed and be carried into the general circulation where it constitutes an embolus.



**Subsequent Fate of the Thrombus.**—Much depends on the presence and degree of infection. If the thrombus becomes septic, *i. e.*, if it is infected with pyogenic bacteria, it will become softened and disintegrated, and may even be converted into an abscess. It is evident that in such a case the patient will be exposed to all the risks of pyemia. As a rule, however, the course is aseptic. *Contraction* of the thrombus occurs owing to the fibrin which it contains. The clot may shrink from the wall of the vein, leaving a space. *Absorption* of part of the thrombus may take place due to the activity of leucocytes. *Organization* is a common occurrence. This begins at the point where the thrombus is attached to the vessel wall. (Fig. 26.) The process is

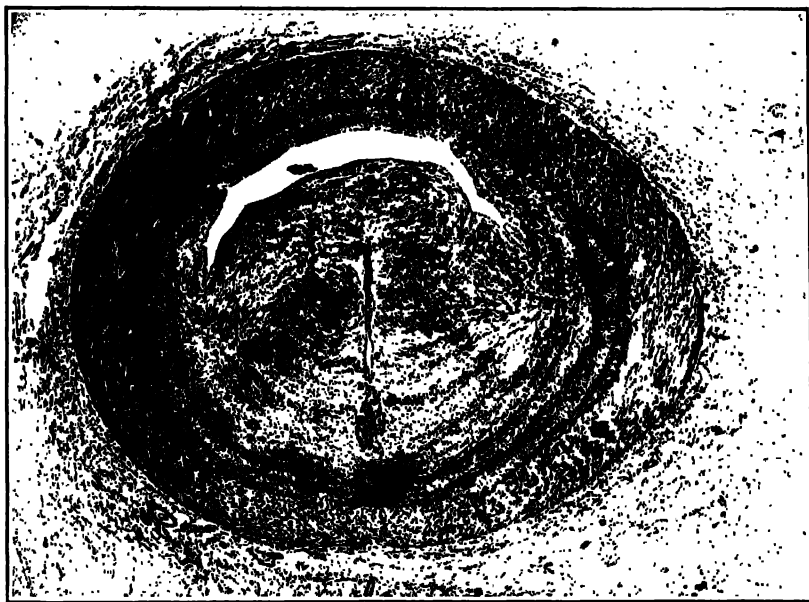


FIG. 26.—Thrombus in artery occluding most of the lumen, and becoming vascularized and organized.  $\times 30$ .

the same as healing in a wound. New capillaries and fibroblasts grow in from the wall of the vessel, a vascular connective tissue is formed, and this is replaced by dense fibrous tissue. New channels may be formed through the fibrous mass and these become lined by endothelium (canalization). (Fig. 27.) If the clot shrinks from the wall of the vessel, the space formed is similarly relined. In this way the circulation may be in part reestablished. Lime salts may be deposited in the thrombus to form a *phlebolith*. These calcified masses are often seen in the pelvic and prostatic veins in roentgen-ray pictures.

**Stasis.**—Kreyberg and other European workers have drawn attention to a condition which must be distinguished from thrombosis, although it is often confused with this process. When a part is chilled,

as in frostbite, the smallest vessels are injured and when circulation is reëstablished they dilate and plasma pours out through their walls owing to increased permeability. As a result the erythrocytes in the minute vessels become conglutinated to form a homogeneous eosinophilic mass which blocks the lumen. Such a mass is commonly referred to as a hyaline thrombus, an unfortunate misuse of a term, for it is in no sense a true thrombus. To this process the name of stasis has been given. (In English and American medical literature stasis signifies merely slowing of the blood stream.) The process is of particular importance in frostbite, where it may lead to necrosis and gangrene owing to the anoxia produced. (See Frostbite, page 333.)



FIG. 27.—Canalization of an organized thrombus in an artery.  $\times 30$ .

### EMBOLISM

An embolus is a solid body which is transported from one part of the circulatory system to another where it becomes impacted. The process is known as embolism. The usual form of embolus is a thrombus which has formed either in the heart or in the bloodvessels and has become detached from the wall. Other forms of emboli are fat globules, air bubbles, tumor cells, and clumps of bacteria. These will be discussed separately. In addition to bloodvessel embolism, some consideration must be given to lymphatic embolism. Embolism is of interest for two reasons: (1) It is the means by which solid material is transported from one part of the body to the other, and is thus of great importance in the dissemination of tumors, bacterial infection, etc.; (2) emboli may produce serious effects at their point of impaction.

*The source of the embolus* depends on the site of the thrombus from which it arises. In the heart there are three sites: (1) the auricle and auricular appendix, (2) a cardiac infarct in the left ventricle, (3) inflamed valves (the vegetations of endocarditis). The veins are of equal importance. Postoperative thrombosis is of special danger, and will be referred to presently in discussing pulmonary embolism. (Fig. 28.) The common sites of venous thrombosis have already been described in the previous section. In embolism following abdominal and pelvic operations the femoral veins must be carefully examined for thrombi. Thrombi in the right and left auricles, particularly in the auricular appendages, are not infrequently the source of emboli. An unusual form is the thrombus which is developed on an atheromatous ulcer in the aorta, and is then carried further into the arterial tree.

**Effects of Embolism.**—The effect produced by an embolus will depend on two main factors: (1) The nature of the embolus; (2) the circulatory arrangements in the organ where the embolus happens to stick.

1. The embolus may be septic or bland. This is a better division than into infected and non-infected, for as an embolus starts as a thrombus, and as a thrombus is so often associated with infection either of a vein or of a heart valve, it is evident that the embolus usually contains some bacteria. It by no means follows that suppuration will develop at the site of impaction of the embolus unless the embolus contains pyogenic micro-organisms. If the embolus is septic, it will give rise to a septic lesion, *i. e.*, an abscess, to which an ischemic effect may be added. If the embolus is bland any effect it may produce is due to ischemia alone.

2. The vascular arrangements of the part are all-important in the case of a bland embolus. When an embolus is impacted in an artery the effect is the same as if the vessel were suddenly closed by a clamp or ligature. This effect may be studied experimentally either by the use of artificial emboli such as seeds injected into the circulation or by clamping or tying the artery supplying the part.

Everything depends on the *collateral circulation*, which in turn



FIG. 28.—Thrombus at site of pelvic operation. Part became detached and caused fatal pulmonary embolism.  $\times 125$ .

depends on the anastomosis between the affected vessel and the neighboring arterioles. In most parts of the body anastomoses are abundant so that when even a large artery is blocked an efficient collateral circulation is soon established; the palmar arch is an example of perfect collateral circulation. Ligature of the femoral artery is at first followed by blanching of the limb which becomes numb and cold. The anastomotic arteries undergo active dilatation, and blood finds its way into the ischemic tissue before any permanent damage is done. The collateral circulation must be maintained, *i. e.*, the dilatation is permanent. The walls of the dilated arteries become thickened to accommodate the increased pressure. It is evident that the efficiency of the collateral circulation will depend on two factors: (1) the state of the vessels, and (2) the strength of the heart. In an old person whose vessels are diseased owing to arteriosclerosis and whose heart is weak, the collateral circulation may be inadequate and gangrene will result. What has been said of ligature of an artery is equally true of obstruction from embolism.

**Infarction.**—An infarct is an area of coagulation necrosis resulting from a sudden arrest of circulation in the artery supplying the part. The word means a stuffing of blood (*infarcire*, to stuff), but this is not an essential feature of the process, depending on the collateral circulation and the looseness of texture of the part. It is only in the lung and the bowel that the part is stuffed with blood. In most of the viscera the anastomoses are less abundant than in the limbs. Cohnheim called these arteries end-arteries, but the term is not strictly accurate; they anastomose with neighboring vessels, but the anastomoses are not sufficient for the needs of the part, and ischemic necrosis results. Moreover the neighboring vessels may be narrowed by arteriosclerosis, so that they are still less able to assist the injured part. This is well exemplified in the case of the coronary arteries.

After a transient initial period of hyperemia the infarct becomes ischemic and pale. The area is wedge-shaped owing to the fan-like distribution of the vessels. The collateral circulation endeavors to pour blood into the part, and owing to dilatation of the capillaries a hemorrhagic border is formed around the infarcted area. If this border is wide enough the entire area becomes hemorrhagic and stuffed with blood. An infarct may therefore be *pale* or *red*, the difference depending on the excellence of the collateral circulation. Infarcts of the kidney and heart tend to remain pale, those of the spleen tend to become red, while in the lung they are always red.

The redness is due to dilatation of the anastomotic vessels. Blood is forced into the collapsed vessels of the ischemic area, so that the part becomes stuffed with red cells. The over-distended vessels may give way, so that hemorrhage occurs. This is most marked in poorly-supported capillaries such as those of the lungs and to a lesser degree in the spleen. In about two hours the red cells become fused together into a homogeneous mass in which their outline can no longer be distinguished.

The tissues in the ischemic area undergo necrosis and die, and within forty-eight hours the infarct of the kidney is completely necrotic. (Fig. 29.) The necrosis is coagulative in type, so that dim outlines of the tubules and glomeruli may remain for a long time. The area is evidently kidney, but it is a city of the dead from which all life and activity have long since vanished. In sections the whole infarcted area stains diffusely with eosin, but at the margin nuclear remains may be seen, and the phenomenon of karyorrhexis is often very well marked. The nuclear fragments are apt to be mistaken for the nuclei of polymorphonuclear leucocytes. At the margin there is an extreme degree of hyperemia, and the hyperemic zone may be of considerable width. The hyperemia may be attributed to the irritation produced by the dead tissue. In old-standing cases a zone of fibrous tissue may be formed around the infarct.



FIG. 29.—Infarct of kidney. The infarcted area is necrotic and is surrounded by a dark zone of congestion. Note the plugged artery.  $\times 8$ .

The gross appearance of an *infarct of the kidney* is very characteristic. (Fig. 30.) An irregular area is observed on the surface, often slightly depressed and surrounded by a pink zone of hyperemia. The cut surface shows an area which may be wedge-shaped or irregular involving the whole width of the cortex and some of the medulla, pale in color and surrounded by a pink border.

In the *spleen* the process is very similar, but the collateral circulation is better, so that the infarct may be either red or pale. Old infarcts, however, are always pale, for the hemoglobin is gradually removed, the red cells disappear, and decolorization takes place.

*Infarction of the heart* is the result of thrombosis of one or more of the coronary arteries; only in very rare instances is it due to embolism.

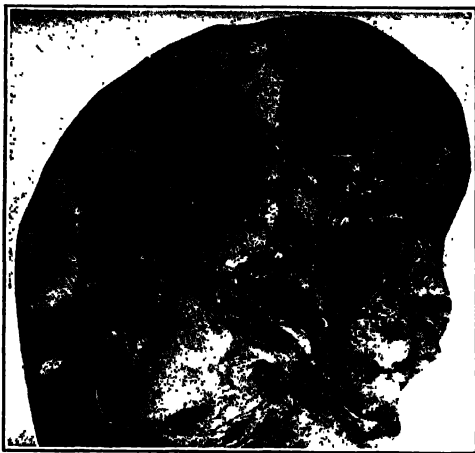


FIG. 30.—Infarct of kidney. There are several pale areas of infarction in the cortex.

It constitutes one of the most important forms of heart disease, and is considered in detail in connection with diseases of that organ.

*Pulmonary embolism and infarction* are naturally very frequent, because an embolus which originates in the veins or in the right auricle will be arrested in the lungs. The condition is of great surgical importance because of the frequency with which it follows operations, especially operations on the female pelvis. In one large surgical clinic it is estimated that 7 per

cent of the postoperative deaths over a series of years were due to this cause. At present we are powerless to prevent or anticipate this complication. It is necessary to distinguish between pulmonary embolism and infarction. There may be: (1) embolism without infarction, and (2) infarction without embolism. (1) A large embolus may occlude the pulmonary artery or one of its main branches (Fig. 31), and the patient dies of shock in a few minutes; in such a case there is no time for an infarct to develop. In a case of suspected pulmonary embolism special care must be taken with the autopsy. The pulmonary artery must be opened with the heart *in situ*, else the embolus is apt to be dislodged. The heart and lungs are then removed *en masse* and the branches of the artery carefully



FIG. 31.—Pulmonary embolism. A twisted embolus occludes the pulmonary artery and its two main branches. The patient died in the course of a few minutes.

opened. A post-mortem clot may be mistaken for an embolus. The embolus is more dry and brittle than the clot, and often shows a twisted, bent, or curled appearance which is very characteristic. In an embalmed body the clot may be as dry as an embolus, but microscopic examination will show the more complex structure of a true thrombus (fused platelets, etc.). (2) On the other hand, an infarcted area, an area stuffed with blood, may be produced by thrombosis of one of the pulmonary veins quite apart from embolism. Postoperative emboli may be divided into three groups: (1) Large emboli which occlude a main artery and cause death with acute respiratory distress in the course of a few minutes. (2) Medium-sized emboli which produce the physical signs of an infarct. (3) Small emboli which give rise to characteristic symptoms (sudden pain in the side, spitting of blood) but no physical signs. The accident usually occurs in the second week of convalescence, but may occur during the first two or three days. Pulmonary embolism may take place in the puerperium.

Belt has shown that pulmonary emboli are even more frequent than had been suspected. By careful dissection he had been able to demonstrate emboli in 10 per cent of autopsies. There is no other autopsy finding which is so easily missed. Embolism was found more often in medical than in surgical cases. In at least 60 per cent of the cases the emboli arose from thrombi in the veins of the leg and pelvis, most of which were unrecognized during life. The deep veins of the calf, which are usually not examined at autopsy, are perhaps the most frequent site of origin of the thrombus. The largest group was that of congestive heart failure—coronary, rheumatic or hypertensive in origin. In most of the cases the venous thrombosis was spontaneous, and unassociated with any apparent inflammation in the veins. In a later communication Belt points out that recovery is not always complete after a non-fatal attack, for organizing emboli may produce cicatricial stenosis of the pulmonary arteries and thus lead to secondary thrombosis.

The use of anticoagulants such as heparin and dicumarol, either singly or combined, has proved of great value in preventing fatal pulmonary embolism. The fatal embolus is often preceded by minor attacks of embolism, or the occurrence of venous thrombosis in the leg may be recognized clinically. Both of these are danger signals which may suggest the use of anticoagulants. Ligation of the veins in the leg has also been used to prevent pulmonary embolism.

Infarcts of the lung are always red because the organ has a double blood supply. Holman has shown experimentally that while small infected emboli introduced into the venous circulation always cause marked changes in the lung in the shape of abscess formation and hemorrhagic infarction, sterile emboli produce practically no evidence of their presence in the deflated lung. When, however, the lung is expanded by inflation the embolic areas can be seen to be paler than the surrounding lung, so that the lung should be inflated at autopsy in examining for sterile embolic areas. The bronchial artery supplies

blood for nutrition at systemic pressure, whereas the pulmonary artery supplies blood for oxygenation at one-third of that pressure. The bronchial artery serves the important function of filling both circulatory beds with blood beyond an embolus. The collateral circulation is therefore abundant. Two results follow from this: (1) Occlusion of a pulmonary artery in a healthy lung is not followed by infarction, because of the abundant anastomosis. If the circulation in the lung is impaired as in chronic venous congestion, embolism readily results in infarction. In postoperative cases, particularly when the abdomen has been opened, there is always such impairment owing to interference with the respiratory movements and to the



FIG. 32.—Infarcts of lung. Two infarcts are seen at the surface of the lower part of the lung. The artery passing to the lower infarct is filled by a pale embolus.

patient lying on his back. (2) The infarct is hemorrhagic and remains red. In course of time the infarct will disappear, but if the lung is inflated and careful search be made, small peripheral scars will often indicate the site of previous infarcts. Castleman has shown that these lesions can be detected in roentgen-ray films as fine white lines, whilst microscopically they can be recognized by the presence of irregular elastic fibers presenting a bizarre curley-cue arrangement. The infarct appears as a firm bright red, wedge-shaped area; the base of the wedge is at the surface and covered by a thin pleural exudate. (Fig. 32.) The pleurisy is the cause of the characteristic pain in the side and the friction rub. The infarct is raised above the surrounding level and



feels firm to the touch. The raised appearance is due to collapse of the surrounding lung when the chest is opened; if the chest is roentgen-rayed before being opened, the infarct will be seen to be depressed, not raised (Castleman). The cut surface is quite dry. The extent of the infarct varies enormously, often quite small, but sometimes involving the greater part of a lobe. Microscopically the alveoli are stuffed with blood, and their outlines are no longer visible, owing to necrosis of the alveolar walls. The presence of blood in the sputum is thus easy to understand.

Should the embolus be septic the element of infarction is obscured by the development of abscesses, usually multiple. The infected emboli may reach the right side of the heart *via* the superior vena cava (septic thrombosis of the lateral sinus and jugular vein, etc.), or *via* the inferior vena cava (septic thrombosis in the puerperal uterus, etc.).

*Infarction of the liver* resembles infarction of the lung in that the infarct is of the red variety and for the same reason, the liver having a double blood supply. It differs from it in being comparatively rare. The embolus originates as a thrombus in a branch of the portal vein (stomach, appendix, etc.) and, as a rule, produces a hemorrhagic bland infarct in which there is little necrosis. If the embolus is septic the result is one or more abscesses of the liver, a condition known as portal pyemia and by no means rare.

*Embolism of the mesenteric artery* leads to infarction of the bowel and constitutes one of the acute abdominal catastrophes. The superior mesenteric is the vessel usually involved. The sudden loss of the blood supply of the bowel wall is followed by gangrene and other consequences which are described in Chapter XX.

*Cerebral embolism* leads to infarction of the brain and subsequent cerebral softening. Necrosis is followed by liquefaction, so that a cyst may be formed.

*Embolism of the central artery of the retina* results in sudden blindness with necrosis of the retina.

**Paradoxical Embolism.** This term is applied to the case where an embolus arises in a vein but lodges in a systemic artery instead of in the pulmonary artery. The occurrence is rare, but an important example of the so-called "crossed" embolism is cerebral embolism with hemiplegia following puerperal thrombosis of the pelvic and femoral veins. The usual explanation given is that the embolus has passed through a patent foramen ovale. If the foramen is really large this is possible, but in many of the cases the foramen is small or completely closed. In these cases the following possibilities may occur: (1) Clumps of bacteria may pass through the pulmonary capillaries and lodge in the cerebral vessels where they set up thrombosis with resulting softening of the brain and hemiplegia. (2) Infarction of the lung which is so common in puerperal thrombosis may cause thrombosis of the pulmonary vessels, and from this an embolus may arise which may pass to the brain. (3) An endocarditis on the left side of the heart may complicate puerperal sepsis, and the vegetations may form emboli which lodge in the brain.

**Retrograde Embolism.**—Retrograde embolism is the plugging of a vein by an embolus moving in a direction contrary to the normal blood flow. Various explanations have been given of this rare occurrence, but none are satisfactory enough to warrant mention.

**Fat Embolism.**—Globules of fat may enter the blood stream and lead to embolism. It is probable that fat gains entrance to the blood very frequently in fractures of bones, in operations on stout people, and in crushing injuries, but corresponding clinical results are uncommon. At the same time, as Warthin points out, the possibility must be borne in mind in all injuries to bone, and the fatal cases have been wrongly diagnosed as shock, coma, concussion, etc. There is no clinical correspondence between the apparent injury and the resulting lipemia which may be fatal. Direct trauma is not necessary, and fat embolism may occur as the result of osteomyelitis, suppuration of fatty tissues, burns of the skin and the convulsions of tetanus, eclampsia, and strychnine poisoning. The introduction of oil into the posterior urethra may cause fat embolism, especially if there has been previous urethral instrumentation, for the posterior urethra is an active absorptive bed. It may follow poisoning by phosphorus and potassium chlorate, and I have seen very exten-

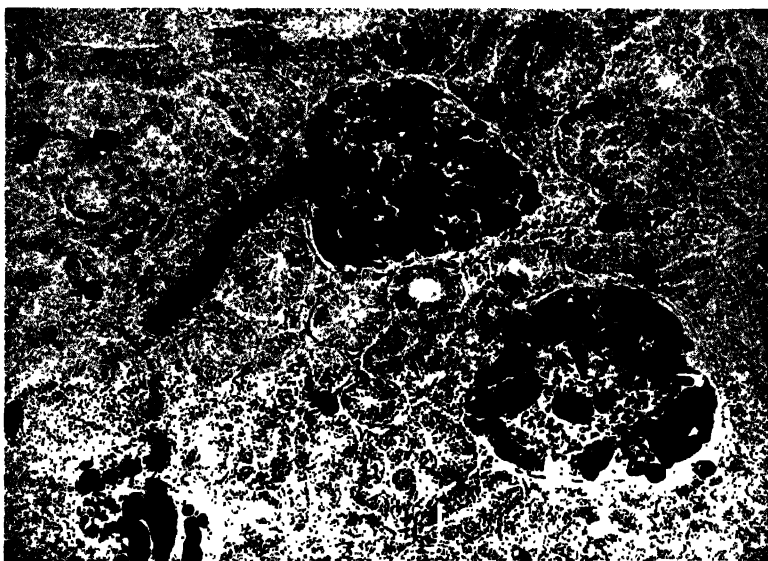


FIG. 33.—Fat emboli in kidney. Frozen section stained for fat.  $\times 100$ .

sive lesions in a young woman who had taken some poison either for suicidal purposes or to produce abortion. The fat enters torn veins, so that globules and cylinders of fat are found in the pulmonary capillaries, but unless frozen sections and fat stains are employed the fat will not be stained. (Fig. 33.) Small globules may pass through the pulmonary capillaries and lodge in the brain, the glomeruli of the kidney, etc. In the kidney the fat globules can be recognized as clear spaces in paraffin sections stained by ordinary methods. (Fig. 34.) Fat regularly appears in the urine, a sign of diagnostic value. An even earlier sign is the presence of free fat and fat-granule alveolar cells in the sputum (Warthin). In the brain there are petechial hemorrhages in the white matter with a fat globule in the center of each. In the few cases in which symptoms appear, these usually come on at twenty-four hours and resemble those of surgical shock with preliminary edema. There may be convulsions and coma from cerebral involvement, and death follows in some of the cases. Fat emboli of the coronary arteries may cause cardiac symptoms.

**Air Embolism.**—Air may enter the circulation as the result of artificial pneumothorax, or if one of the large veins in the neck is opened during an operation, etc. It occurs about once in every 500 to 1000 pneumothorax treatments. In the vast majority of cases no harm results. The rare fatal cases may be due to the air converting the blood in the heart into a froth which makes proper cardiac contraction impossible, or bubbles of air may reach the brain. It is when a vein is only partially severed thus preventing its collapse, that there is danger of air embolism. This is particularly true of the large veins in the neck where there is marked negative venous pressure. When a vein in the neck is cut in the course of an operation on the thyroid, the first sign is a hissing sound in the wound, the so-called "sifflement," as air is sucked in. The result is dyspnea, cyanosis, coma, and finally death. Many cases are due to the injection of air, with or without fluid, into the uterus in the production of criminal abortion; the placenta becomes separated, and air enters the large uterine veins. My colleague Dr. W. L. Robinson has seen 5 such

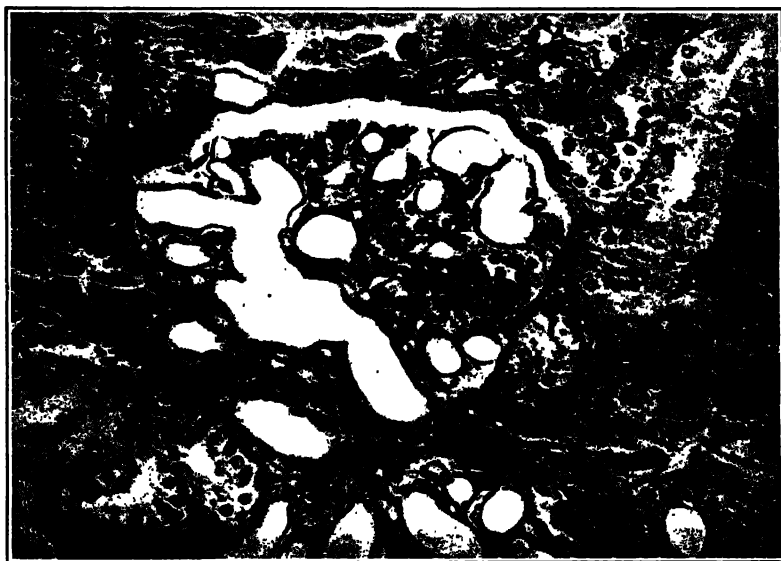


FIG. 34.—Fat emboli in kidney. Paraffin section. The spaces represent fat which has been dissolved out.  $\times 200$ .

cases in a comparatively short period. In these cases the inferior vena cava is distended with bubbles of air, and should be inspected before the heart is removed. In opening the heart in a case of suspected air embolism special precautions must be taken. All vessels entering the heart must be tied before it is removed, and it must be held under water when the chambers are incised, so that any bubbles of escaping air may be detected.

**Caisson Disease.**—Caisson disease in which air embolism is largely responsible for the symptoms is considered in Chapter XII.

**Tumor Emboli and Bacterial Emboli.**—These need only be mentioned. The former is discussed in connection with tumors, the latter in connection with pyemia.

**Lymphatic Embolism.**—Tumor cells may be carried along lymph vessels to the regional lymph nodes. Clumps of bacteria may pursue the same route. When the normal channels are blocked, as in carcinoma and tuberculosis, the emboli may pass along channels in a direction opposite to that of the normal flow; this is a form of retrograde embolism.

### EDEMA

Edema is a singularly complex subject, the fundamental principles of which until recently have been little understood. There are several forms of edema, only one of which is directly connected with circulatory disturbances. Nevertheless it is convenient to discuss the whole subject here. The question of the regulation of water exchange is not included in this discussion.

Edema or dropsy is an abnormal accumulation of fluid in the tissue spaces and serous cavities. This accumulation may be local or general, a distinction of great importance; in the former the causal factor is local, in the latter it is general. When water collects in the tissues it may be in free or combined form. When combined it is united with the protoplasm of the tissue elements. When free it lies between these elements and can be moved from one place to another. For this reason a pit is left when an edematous part is pressed on; this is known clinically as "pitting on pressure." Sometimes there is a solid edema, in which case there is no pitting on pressure. The water is taken up mainly by the connective tissue of the muscles and skin, or rather the subcutaneous tissue. An initial accumulation of water cannot be detected clinically. Indeed it is only when 5 or 6 liters have collected in these water depots that edema becomes evident. But this invisible accumulation of fluid is indicated by a steady increase in weight.

The volume of water in the blood must be kept constant, so that it is not allowed to accumulate within the vessels. When a person drinks a large quantity of water it is absorbed in the blood, but rapidly passes out into the tissues and is retained in the water depots. It must be remembered that in a person of average weight there are 35 kg. of water in the body, but that only 5 of these are in the blood while 30 are in the tissues. As the kidneys excrete water from the blood, the water in the tissues passes back into the blood. The water in its passage must traverse the walls of the capillaries. Some of the fluid in the tissues is carried off by the lymphatics. It will thus be seen that the amount of fluid in the tissues depends on the following factors: (1) the amount of fluid ingested; (2) the condition of the capillary walls, with which may be included the condition of the general circulation; (3) the condition of the tissues (distribution of electrolytes, concentration of sodium chloride, degree of oxygenation, amount of acidosis, etc.); and (4) the condition of the kidneys. There is in addition the question of a nervous regulatory mechanism of water exchange which may be disturbed. The complexity of the problem now becomes evident, and the impossibility of stating with certainty which factor or factors are at fault in any particular case.

Edematous fluid closely resembles lymph; the one is normal, the other abnormal, interstitial fluid. It contains less proteins, and the specific gravity is lower—1.006 to 1.012. It does not readily coagulate when removed from the body, but sometimes a thin clot may form. No clotting occurs within the body (*e. g.*, in the serous cavities). At

the same time it must be recognized that the composition varied with the mode of production and the etiological agent. A distinction may be drawn between a transudate and an exudate. A *transudate* is ordinary edematous fluid; the specific gravity is below 1.015 and the protein below 3 per cent. An *exudate* is the fluid of an inflammatory edema; the specific gravity is above 1.018, and the protein above 4 per cent. Clotting is more marked when the fluid is removed from the body, and may occur within the serous cavities. It is evident that an exudate more closely resembles blood plasma than does a transudate.

*Tissue Changes.*—An edematous tissue has a pale watery appearance. Subcutaneous tissue may come to resemble jelly. In the lung where edema of the alveoli is very common, the affected part may feel solid, but fluid pours from the cut surface. The brain acquires a characteristically wet appearance. Under the microscope the tissue elements are widely separated by watery material which can be best demonstrated if the tissue is fixed in boiling formalin so that the fluid does not escape. In well-fixed specimens the fluid appears as fine granules. The fluid of edema is not always intercellular. Cells and fibrin may become edematous and swollen; the change is similar to hydropic degeneration.

**Varieties of Edema.**—Fluid may collect in the tissues under a variety of conditions which bear no relation to one another. Edema may be local or general. Of course, in general edema the condition may be more pronounced in one locality, but the etiological agent acts generally. The main forms of edema are *inflammatory*, *obstructive*, *cardiac*, and *renal*. Inflammatory and obstructive edemas are local, cardiac and renal edemas are general. To these must be added *angioneurotic* and allied forms of edema; also the edema of *chronic starvation* and that variety of it known as *wax edema*. Instead of taking these up *seriatim* it will be better to consider the various factors which may cause edema, and then return to the special forms of the condition.

**Causes of Edema.**—There are three main causes of general edema, and a fourth factor which comes into play in local edema. In addition to these there are a number of secondary factors which will have to be considered. The primary factors in general edema are: (1) Increased permeability of the capillary wall, (2) decrease of the colloid osmotic pressure of the plasma proteins, and (3) increase of the capillary blood-pressure. The additional factor in local edema is (4) lymphatic obstruction.

1. **Increased Permeability of the Capillary Wall.**—The normal capillary wall is a semipermeable membrane through which water and salts can pass in either direction with the greatest ease. Much has been written about increased permeability of the vessel wall as a cause of edema, especially in inflammation. The endothelial wall cannot become more permeable to water and crystalloids, because it already is completely permeable. Moreover, the rate of passage of these materials and their amount is independent of the condition of the capillary wall, being determined entirely by forces on either side of the wall, either in the

blood or in the tissues. But the outward passage of colloids is intimately related to the condition of the vessel wall. Under normal conditions protein is prevented almost completely from passing from the blood into the tissues, but when the vessels are injured by toxins, lack of oxygen, etc., they become readily permeable to protein, as is seen in-inflammatory edema. In the kidney this causes albuminuria, while elsewhere there is what Eppinger has called "albuminuria into the tissues." The passage of the large protein molecules is favored by dilatation of the capillaries, due in turn to relaxation of the branching Rouget cells, and Krogh believes that this is one of the major factors responsible for the great escape of protein in the edema of inflammation.

The escape of protein is of the greatest importance in the production of edema, for it lowers the colloid osmotic pressure of the blood and raises that of the tissues, as a result of which water readily passes out through the capillary wall. The increased permeability to protein is thus a major factor in the production of edema.

## **2. Decrease of the Colloid Osmotic Pressure of the Plasma Proteins.—**

We have seen that the water of the blood can escape with the greatest ease into the tissues. The force which holds it back is the colloid osmotic pressure of the proteins. If an animal is bled repeatedly but kept alive by reinjection of the red blood cells, the plasma proteins will fall to a low level and marked edema will develop. A fall of plasma protein below 5 per cent will cause edema. For this reason long-continued anemia is apt to be associated with edema. Marked ascites, when the fluid is rich in protein, as in malignant disease of the peritoneum, may lead to generalized edema (anasarca) owing to the severe plasma-protein loss. The different proteins of the plasma have different colloid osmotic pressures, albumin being about four times stronger than globulin. It follows that when there is a great loss of albumin from the blood, as in the albuminuria of chronic Bright's disease (wet nephritis, nephrosis), with a reversal of the normal albumin-globulin ratio (3 to 1), edema will result. The colloid osmotic pressure depends therefore partly on the total amount of plasma proteins, partly on their relative proportion.

## **3. Increase of the Capillary Blood-pressure.—**

The pressure in the capillaries is the force which overcomes the colloid osmotic pressure of the plasma and enables the normal passage of nutritive fluid into the tissues. If it is increased, edema will result. The pressure in the capillaries depends upon the venous blood-pressure and not upon the arterial pressure. In cardiac failure the venous pressure rises markedly, and the increased capillary pressure leads to edema. The stretching and dilatation of the capillaries also renders them more permeable. The edema which follows thrombosis of the main vein of a limb is largely due to an increase in the capillary blood-pressure. It must not be thought, however, that fluid can only leave the blood through the capillaries. Rous and his associates have shown that in the case of the skin the permeability of the vessels to a slowly diffusible vital dye is much greater in the venules than in the capillaries. There is a

mounting grade of permeability along the capillaries, being lowest at the arterial and highest at the venous end.

4. **Lymphatic Obstruction.**— This is an important factor in the production of local but not general edema. Much of the intercellular fluid in the tissues escapes by way of the lymphatics, so that obstruction to outflow through these channels will cause local edema. The obstruction may be due to inflammation, the presence of tumor cells within the lumen, or *Filaria bancrofti*, a parasitic worm which may block the channel. Pressure from without produces the same effect. This pressure may be due to a tumor or to collection of fluid. As the fluid increases the lymphatic obstruction becomes more marked, so that a vicious circle is formed. For this reason removal of part of an effusion in a serous sac is often followed by disappearance of the remainder, for reduction of the pressure allows the lymph channels to be opened up and the fluid to be drained away. Examples of lymphatic edema are the swelling of the arm which may develop in cancer of the breast; *elephantiasis* or swelling of the legs, scrotum, etc., seen in most marked form in obstruction due to filaria; *chylous ascites* and chylothorax, effusions of chylous fluid in the abdominal and pleural cavities due to obstruction of the thoracic duct by filaria, tumors, enlarged glands, etc. *Non-parasitic elephantiasis* is an edema of the leg occurring mostly in young women, due apparently to chronic lymphangitis of unknown origin. *Milroy's disease*, or hereditary edema, is also probably lymphatic in origin.

*Secondary factors* are the osmotic pressure in the tissues and chloride retention due to renal insufficiency. It is evident that if the protein of the plasma escapes through the capillary wall the *colloid osmotic pressure of the tissue* will rise, and on that account water will pass out of the vessels. *Chloride retention* is a secondary but not a primary factor; it aggravates and continues an already existing edema, but does not initiate the condition. It used to be thought that the edema of Bright's disease was due to retention of the chlorides in the tissues owing to inability of the kidneys to excrete them. This popular fallacy is now exploded. Removal of the kidneys or mechanical obstruction of the urinary passages is followed by complete salt retention and an enormous accumulation in the blood and the tissues, yet no edema develops. Moreover the kidney in wet nephritis is quite able to excrete salt. The salt is retained because of some extrarenal factor. But although salt retention is not a primary factor in the production of edema, yet once the condition of edema is established and the chlorides pass into the tissues with the water, the greater the amount of salt available, the more water will be retained in the tissues because of the increase of the osmotic pressure there. That there is a real relation between salt retention and edema is shown by the fact that in renal edema the withdrawal of salt from the food is often followed by rapid disappearance of the edema and a corresponding increase in the flow of urine. Martin Fischer's idea that the chief cause of edema is an increased water-binding power (hydration capacity) of tissue

colloids owing to an accumulation of acid products the result of insufficient oxygenation, although attractive because of its simplicity, has had to be abandoned for the present.

Elwyn points out that there is a unitary mechanism for maintaining a constant volume of water in the blood, the chief parts of this mechanism being the muscles and skin which act as water depots and the kidneys which excrete the water. This mechanism appears to be under the influence of a nervous center in the hypothalamic region of the cerebrum. Disturbance of this center may thus alter the water balance.

With these additional facts in mind we may briefly review some of the various forms of edema which have already been mentioned.

**Inflammatory Edema.**—The swelling which is one of the cardinal signs of inflammation is largely due to edema. Owing to the action of the irritant the permeability of the capillaries is increased and fluid pours out into the intercellular spaces. This fluid is rich in protein. Owing perhaps to the formation of a network of fibrin the fluid cannot be moved about through the tissues as in other forms of edema, nor is it influenced by gravity. There are other factors besides injury to the vessel walls, but these and other matters connected with the edema of inflammation are discussed in detail in the next chapter. If the inflammation involves the pleura, pericardium, or peritoneum these serous sacs are filled with fluid from which fibrin is deposited on the surface.

**Cardiac Edema.**—This might better be called congestive edema, for it is apt to develop in any long-standing condition of venous congestion, though usually due to progressive cardiac failure. The obstructive edema seen when a large vein becomes thrombosed belongs to the same group. The fluid is loose in the tissues and readily changes its position under the action of gravity, so that it first appears in the dependent parts. The serous sacs become filled with fluid. For some reason the effusion is much commoner in the right pleural sac than in the left. Several factors are probably at work. Owing to the failing circulation there is an increase of pressure in the veins and capillaries. For the same reason there is back pressure in the lymphatics. The capillary walls are stretched and rendered more permeable. Oxygenation is poor and the vascular endothelium suffers in consequence and fails to hold back the water, but this factor is probably not of much importance, else the proteins would come through in larger amounts.

*Pulmonary edema* is a variety of cardiac edema. As the left side of the heart fails, blood accumulates in the lungs and fluid passes from the distended capillaries into the alveoli. The condition is most marked in the dependent parts of the lung. The changes are described in the section on the Lungs.

**Renal Edema.**—This resembles cardiac edema except that the fluid is less influenced by gravity. Nor are the serous sacs involved so soon. The protein content and specific gravity are much lower than in cardiac edema, indeed lower than in any of the edemas. Blood examination



will at once differentiate the two, for in edema due to chronic nephritis the blood cholesterol is markedly raised, while in cardiac edema it is normal. Renal edema is seen in acute nephritis, in the subacute or wet stage, and in the condition known as nephrosis, which is probably merely a variant of true nephritis. In all of these the edema is associated with marked albuminuria but not with a high blood-pressure. Indeed as the blood-pressure goes up the edema tends to disappear. A number of factors appear to be responsible. In wet nephritis and nephrosis there is a fall in the blood proteins and a reversal of the normal (3 to 1) albumin-globulin ratio; both of these reduce the osmotic pressure in the blood so that water passes into the tissues. Crystalloids, especially sodium chloride, are retained in the tissues and raise the osmotic pressure there, so that when water is drunk it passes into the tissues instead of into the urine, what Fishberg calls a prerenal deviation of water.

**Cachectic Edema.**—In many wasting diseases and anemias edema develops in the later stages, affecting the feet and legs particularly. Several causal factors may be at work. There is likely to be cardiac exhaustion and circulatory failure, the nutrition of the vessel walls is interfered with, the blood proteins especially in anemia are lowered and the osmotic pressure falls.

**Famine Edema.**—In prolonged undernutrition and chronic starvation edema may develop. This was common among prisoners on the Continent during the World War. The blood proteins are very low owing to absence of proteins from the diet, so that the osmotic pressure falls and fluid leaves the blood-vessels. It is probable that absence of vitamin A has something to do with it, because in many cases there develops the ulceration of the cornea (xerophthalmia) characteristic of deficiency of that vitamin.

**Neuropathic Edema.**—Nervous disturbances appear to play a part in the production of some edemas. When the femoral vein is tied there is no edema, but if the sciatic nerve is also cut the vasoconstrictor impulses are also removed and edema develops. Edema may occasionally develop in nervous disorders, the best-known form being *angioneurotic edema* in which there is a sudden though transient edema affecting one area of the body (arm, etc.). Recent work suggests that this is a manifestation of allergy, a hypersensitiveness of the vessels to some circulating protein, but this theory cannot be regarded as proved.

**Hereditary Edema. Milroy's Disease.**—This is a chronic edema without any evident cause or constitutional disturbance. It is markedly hereditary. Milroy observed 22 cases in a family of 97 individuals (six generations). It is confined to the lower limbs, affecting one or both legs. The leg may be very greatly swollen. The condition should be distinguished from the non-parasitic form of elephantiasis, a condition which is usually confined to women, whereas Milroy's disease is equally common in both sexes.

## SHOCK

The basis of shock is essentially a circulatory disturbance, so that it may be considered here. This mysterious and sinister condition is liable to develop after: (1) extensive operations, particularly those involving handling of the abdominal viscera; (2) acute abdominal catastrophes (perforation of stomach or bowel, strangulated hernia, acute pancreatitis); (3) severe injuries; (4) extensive hemorrhage.

The condition has continually to be guarded against by the surgeon, and is of special importance in war injuries.

The appearance of a person in shock is characteristic. He lies quite still, apparently unconscious of his surroundings, but can answer questions slowly and correctly. The face is pale and gray, drawn and anxious, and the skin is cold and clammy. The temperature is subnormal, the pulse feeble, the respirations shallow and sighing, and the blood-pressure alarmingly low. Shock fortunately may be only a temporary condition; it is a step toward death, but a step which the patient can retrace in a few hours.

**Causes.**—Moon puts the matter in a nutshell when he remarks that the shock syndrome results from a disparity between the volume of blood and the volume-capacity of the vascular system. There may be a decrease in the blood volume, an increase in the volume-capacity of the vascular system, or a combination of these. The blood volume may be decreased by hemorrhage, and by transudation of serum through the capillary walls with resulting increased concentration and viscosity of the blood and rise in the red cell count and hemoglobin percentage (an important factor in shock due to severe burns). Shock is a circulatory deficiency characterized by decreased blood volume, decreased cardiac output, and increased concentration of the blood.

A distinction must be drawn between *primary shock* which follows immediately on the receipt of a severe injury and *secondary shock* which may not develop for twenty-four hours. In primary shock the chief factor is the discharge of nociceptive nervous stimuli which lead to *widespread capillary paralysis*. In secondary shock the commonly accepted explanation of the capillary paralysis is the widespread action of a histamine-like substance liberated as a result of the bruising of muscles. During the World War Bayliss and Cannon showed that experimental bruising of muscles in animals was followed by shock, but if the main vessels of the limb were first tied no shock developed. Injection of extract of the bruised muscles produced the same effect. Dale has shown that the *injection of histamine*, a cleavage product of protein produces an identical result. The observations of Blalock have thrown doubt on this explanation of secondary shock. Blalock points out that bruising of muscles is accompanied both by hemorrhage into the part and by a great extravasation of serum due to increased permeability of the capillaries. There is therefore a great decrease in the volume of the blood with resulting shock. *Accessory factors* undoubtedly play a part. Thus cold, exhaustion, depression, and general anesthesia (especially ether and chloroform) predispose to the development of shock.

**Nature of Shock.**—Shock, like eclampsia, might be called “the disease of theories,” and several pages might be filled in discussing them. It is probably a mistake to look for a single causal factor; in most cases of shock in man a variety of factors come into play. The essence of the condition seems to be a relative disappearance of blood from the heart and great vessels, so that the heart has not sufficient

fluid on which to contract. Much used to be written about "the mystery of the lost blood." In shock due to hemorrhage there is of course no mystery. In other cases it is now known that the blood has disappeared into the vastly dilated capillary bed or into the tissues owing to transudation of serum. The patient may therefore be said to bleed into his own capillaries or into his tissues. In a state of health only a small amount of the capillary bed is open at any one time. The blood flows through only a limited number of glomeruli in the kidney at the same time. According to Krogh the volume of blood in the active muscles of a guinea-pig may be 275 times as great as when the muscles are at rest, and if the entire capillary bed were opened up there would be 750 times as much blood. If, then, something can paralyze the vast capillary bed of the body and cause it to dilate, the blood will disappear into it as if sucked up by a sponge, the blood-pressure will fall, the heart will be unable to beat properly, and the brain will suffer from anemia.

The *lesions* are those which might be expected from these general considerations, as Moon has shown both in the experimental animal and in man. They are most marked in the lungs and the gastro-intestinal tract. The lungs are dark and filled with blood. The liver and gastro-intestinal tract are intensely congested. All this is in marked contrast to surface structures, which are pale and bloodless. Microscopically the pulmonary capillaries are widely dilated and the alveoli are filled with fluid; it is a picture of pulmonary congestion and edema. In the wall of the intestine the increased capillary permeability is evidenced by petechial hemorrhages and edema. Similar lesions are found in fulminating influenza and severe burns, conditions in which the clinical picture is one of shock. The lesions are thus the reverse of those seen in severe hemorrhage.

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## CHAPTER IV

### INFLAMMATION

INFLAMMATION is the most common, the most carefully studied, and the most fascinating of the changes which the body undergoes as the result of disease. Its history is the history of pathology. For two thousand years it remained an enigma. Not until Virchow laid the solid foundation of modern pathology by his doctrine of Cellular Pathology was it possible to solve the riddle of the sphinx. And yet at the present day there is no subject in the whole of pathology which is more thoroughly understood, although there are still many fundamental problems which demand investigation. "For the development of the sound pathologist," as Adami remarks, "a full knowledge of the factors concerned in the inflammatory process and a right appreciation of the doctrine of inflammation is as essential as to the orthodox theologian is a right attitude in respect to the doctrine of the Trinity."

**Definition.** Inflammation is the local reaction of the body to irritation. There is a general reaction which will be considered later under the heading of Infection. The local inflammatory reaction presents two phases. The object of the first is to destroy and remove the irritant; the object of the second is to repair the damage done to the tissues. The first is subserved by the wandering mesodermal cells whether of the blood or the tissues, the second by the fixed cells of the part. Many pathologists confine the term inflammation to the first of these processes, considering the second as a manifestation of repair. Such a procedure is quite justifiable, but we prefer to adopt the wider conception. Degeneration of varying degree is always present. The histological picture of inflammation is therefore made up of three features, although differing greatly in intensity; these features are degeneration, exudation and proliferation.

**Causes.**—From our definition it is evident that any irritant may act as a cause of inflammation, so that a full list of causes would include every known irritant. These irritants may be divided into two great groups, the living and the non-living. Of the *living* irritants by far the most important are the pathogenic or disease-producing microorganisms. Of less importance are the animal parasites. Both of these act as irritants mainly by virtue of chemical poisons which they produce, and to a lesser degree by the mechanical irritation which they excite. The pathogenic bacteria usually excite an acute reaction, as a result of which both the cells and the fluid part of the blood pass from the vessels into the tissues. Some produce a more chronic form of reaction, characterized in the main by proliferation of the tissue cells; examples of such chronic irritants are the microorganisms of

tuberculosis and syphilis. The *non-living* irritants may be divided into physical and chemical. Among the *physical* irritants may be mentioned trauma, the presence of a foreign body, the action of undue heat and cold (burns and frostbite), of pressure, of light, of electricity, of roentgen-rays, of the radiations from radium, etc. *Chemical* irritants include strong acids and alkalis, and poisons of every description.

In the discussion which follows it should be borne in mind that there is no hard and fast line between an irritant and a stimulant. If an irritant is sufficiently weakened it becomes a stimulant. It follows, therefore, that while at the center of the inflammatory stage we shall find every evidence of intense irritation, away at the wings the tissues may respond as to a stimulant.

**The Essence of Inflammation.**—The word inflammation takes us back a long way in the history of medicine. Literally it means a burning. The condition was studied clinically hundreds of years before any true insight was obtained as to the inner pathological meaning of the process. It was Celsus in the first century A.D. who named the famous “cardinal signs” of inflammation as *calor*, *rubor*, *tumor* and *dolor* in words which have subsequently become celebrated: “Now the characteristics of inflammation are four—redness and swelling, with heat and pain.” In the course of time it became evident that these cardinal signs were the outward expression of vascular changes. In the middle of the nineteenth century Cohnheim applied the experimental method to the study of inflammation and showed with a brilliance and conclusiveness which left no room for doubt the all-important part played by the vessels in the process.

But the vascular changes are not the essence of inflammation. It remained for Metchnikoff in 1892 to demonstrate in his great work on the Comparative Pathology of Inflammation that the central theme of inflammation was the reaction of the wandering mesodermal cells against the irritant. In the higher animals which possess a vascular system these cells are for the most part contained within the blood-vessels. They are the leucocytes of the blood. The object and meaning of the vascular phenomena is to bring these mesodermal defense cells from the interior of the vessels to the outside where they can meet and cope with the irritant. The vascular changes are very striking, for the clinician they provide the cardinal signs of inflammation, but they are not essential.

This becomes evident when we turn to the study of inflammation in animals without a vascular system and in non-vascular tissues such as the cornea. The wandering cells of the part gather around the irritant and cope with it just as surely as if they had come from the interior of the vessels. Metchnikoff made his fundamental observations on the transparent body of the larva of the starfish. Introducing some rose-thorns beneath the epidermis, he found next morning that they were clustered around the amoeboid mesodermal cells, which fused into a plasmodial mass that shut off the irritant from the body cavity. When bacteria were introduced they were taken up by the

mesodermal cells, ingested, and destroyed. This is the simplest possible example of the reaction of a multicellular organism to an irritant. It is an example of the essence of inflammation. Metchnikoff observed, moreover, that in the starfish larva, in the water-flea (*Daphnia*), and in other transparent bodies, whenever the injury ceased to progress reparative changes set in, changes which were not confined to the mesodermal cells, but involved all the cell layers. Even in the lowest forms of life, therefore, irritation excites repair as well as inflammation in the narrower sense of the term.

In the *non-vascular tissue* of higher animals the same sequence of events may be observed. The most convenient tissue for this purpose is the cornea. If the cornea be lightly cauterized in its center or if bacteria be introduced, the first result is death of the corneal corpuscles at the site of injury. Soon, however, a change may be noticed in the corpuscles lying at a distance. They become enlarged, undergo division, throw out processes, and move to the site of irritation. This defense reaction is followed by repair.

In man and other vertebrates the mesodermal cells of defense may be divided into the wandering cells of the blood (the leucocytes) and the resting wandering cells of the tissue. It is the former which play the major part in the earliest stages of acute inflammation. Moreover there is a humoral factor of defense as well as a cellular factor, and the constituents of the humoral factor are contained in the blood plasma. It thus becomes necessary for both the white blood cells and the blood plasma to escape from the interior of the vessels in order that they may reach the irritant. This escape is brought about by the vascular phenomena of inflammation.

**The Vascular Phenomena.**—We owe our present complete knowledge of the vascular changes in inflammation to the experimental researches of Cohnheim, whose *Lectures on General Pathology*, published in 1877 and now available in English translation, should be consulted by anyone interested in inflammation. It is remarkable how little has been added by subsequent observers.

Cohnheim's method was to draw out the intestine of a curarized frog through an opening in the abdominal wall and spread the mesentery on the stage of the microscope. Or he shaved off the papillary surface of the frog's tongue and observed the vessels in the base of the wound. Or the web of the foot may be used to which a mild irritant such as dilute acetic acid is applied. Whichever of these methods he employed, soon, as Cohnheim remarks, "a succession of appearances will be developed which are well calculated to fully engross your attention."

There may be a brief contraction of the vessels due to the stimulating effect on the vessel wall produced by the irritant when still weak in its action, but the first thing to attract attention is a dilatation of the exposed vessels, most marked in the arteries, then in the veins, and last of all in the capillaries. This paralytic dilatation is accompanied by a temporary acceleration of the blood stream, followed later

by slowing. At this stage the vascular dilatation is very marked and innumerable capillaries come into view, because though previously empty they are now filled with blood, so that the active capillary bed is greatly increased and the vascularity of the part may actually be doubled. The increased vascularity is responsible for such cardinal signs as ~~redness, swelling and heat~~. The slowing of the blood stream in the still dilated vessels becomes more and more marked, and if the action of the irritant is sufficiently intense there may be complete stasis or stoppage of the local circulation, with clotting (thrombosis) of the blood. The effect of the thrombosis is disastrous, for the tissues cannot survive when their blood supply is cut off, and death of the part (necrosis or gangrene) is certain. In the slower blood stream it now becomes possible to distinguish the individual corpuscles. It is then seen that a rearrangement of the formed elements of the blood has taken place. Under normal conditions the red and white cells flow intermingled in the central part of the vessel, forming an *axial stream* which is separated from the wall of the vessel by a clear *plasmatic zone* free from cells. In the veins of the inflamed part the leucocytes fall out of the axial stream and come to occupy the plasmatic zone. They tend to adhere to the vessel wall, and seem to drag themselves along with difficulty. In this way the inner wall of the vein becomes paved by an unbroken line of leucocytes without the admixture of a single red blood cell. This arrangement is spoken of as the *pavementing* of the leucocytes.

What follows next can best be described in the vivid words of Cohnheim himself. "But the eye of the observer hardly has time to catch all the details of the picture before it is arrested by a very unexpected occurrence. Usually it is a vein with the typical peripheral arrangement of the white corpuscles, but sometimes a capillary, that first displays the phenomenon. A pointed projection is seen on the external contour of the vessel wall; it pushes itself further outwards, increases in thickness, and the pointed projection is transformed into a colorless rounded hump; this grows longer and thicker, throws out fresh points, and gradually withdraws itself from the vessel wall, with which at last it is connected only by a long thin pedicle. Finally this also detaches itself, and now there lies outside the vessel a colorless, faintly glittering, contractile corpuscle with a few short processes and one long one, of the size of a white blood cell and having one or more nuclei, in a word, a colorless blood corpuscle."

This mechanism by which the white blood cells pass through the walls of the vessels is known as the *emigration* or *diapedesis* of the *leucocytes*. It is confined to the veins and in a lesser degree to the capillaries. The contour of the arteries remains smooth as before, nor can any leucocytes be seen adhering to their outer surface.

It is not only the leucocytes which appear outside the vessel walls. Numbers of red cells may follow in their wake, but these numbers vary widely, depending on the nature of the irritant. No openings can be demonstrated in the capillary wall after the erythrocytes have



passed through. It may be that they close immediately. Or it is possible that the colloid protoplasm of the red cell simply flows through the endothelial cell, leaving no trace of its passage. When the red cells are very numerous the inflammation may be called *hemorrhagic* in type. If the walls of the capillaries give way small hemorrhages known as *petechiæ* may occur.

The vascular endothelium does not remain passive during this period of excessive activity. The lining cells become enlarged and proliferate, they assume a rounded form so as to project into the lumen of the vessel, and they exhibit amœboid movement. In sections of inflamed tissue this swelling of the endothelium is a striking feature (Fig. 35), and if the observer is fortunate he may detect evidence of cell division (mitosis). The result of these changes is twofold. First, the obstruction offered to the blood stream is an important factor in retarding the flow, and second, the swelling of the cells probably facilitates the passage of the leucocytes between them. The sharpness of outline of the individual elements which constitute the vessel is lost, the wall has become looser in texture, and its outer limit is nebulous. Through this protoplasmic sponge the polymorphonuclear leucocytes can be observed making their way, just as they may be seen to pass between the epithelial cells of an inflamed mucous membrane or even through the stratified epithelium of the skin, appearing unexpectedly on the intact surface. (Fig. 36.)



FIG. 35.- Swollen endothelial cells with leucocytes passing between them.  $\times 1300$ .

Burrows, in his suggestive monograph on The Localization of Disease, lays great stress on increased capillary permeability. He considers that the essential vascular factor in inflammation is increased permeability of the injured cells, as the result of which substances can more freely enter and escape from the cytoplasm. The most permeable section of the small vessels appears to be the part where the capillaries terminate in the venules. Diapedesis begins in the smallest veins and then in the venous ends of the capillaries. It is at this point that oxygen tension is at its lowest, and the resistance of capillary endothelium to permeation depends on an adequate supply of well-oxygenated blood. The diapedesis of particles is probably due

to differences of electrical potential, for all migrating particles carry negative charges, and are attracted to any tissue which is relatively electro-positive.

The outward movement is not confined to the solid particles of the blood. The blood plasma also passes out into the tissues, the amount varying much with the nature of the irritant. In the tissues it may be responsible for much of the swelling, causing an inflammatory edema. The subject of the plasma in the tissues will be taken up when the inflammatory exudate is considered.

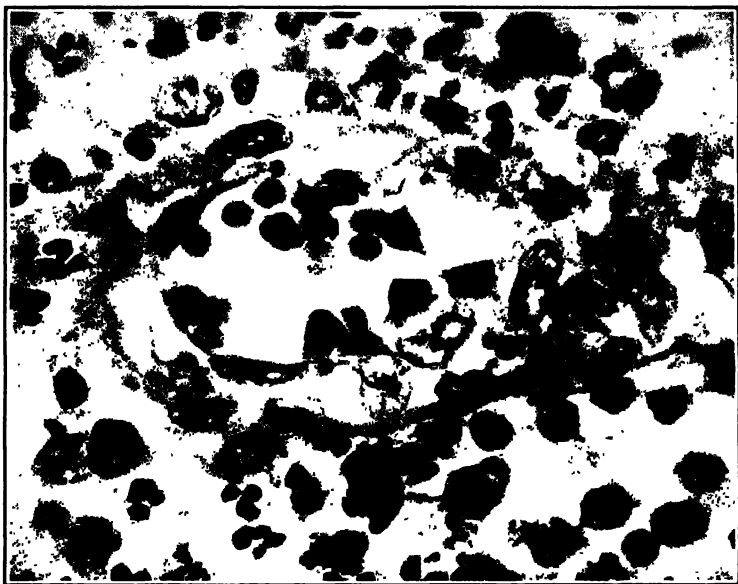


Fig. 36.—Separation of elements of vessel wall; emigration of leucocytes.  $\times 800$ .

In inflammation there is not only an opening up of preëxisting capillaries but also a formation of new vascular channels. This is accompanied by new formation of lymphatic capillaries (Pullinger and Florey). An astonishingly rich plexus of lymphatics is formed by the end of ten days. These vessels are only visible when injected owing to the colorless nature of their contents. They disappear as healing occurs.

*The Influence of the Nervous System.*—The vascular changes, both dilatation and exudation, are influenced by nervous impulses. If in one ear of a rabbit the vasoconstrictor nerve be cut and in the other ear the vasodilator nerve, and inflammation of both ears be then produced by means of hot water, a marked difference in reaction on the two sides can be observed. In the ear where the constrictor fibers are cut hyperemia is marked and complete recovery ensues. In the ear where the dilator fibers are cut the vessels remain constricted,

stasis soon develops, and there will be a considerable amount of necrosis of tissue. When the nerve to a part is divided the normal constrictor impulses are cut off, and inflammation develops much more rapidly than usual. In such a part the capillaries permit a greater emigration of leucocytes and a greater transudation of lymph through their walls.

It is evident that the more rapidly and completely a condition of hyperemia can be induced, the more satisfactory will be the inflammatory response, the less damage will be done, and the more complete will be the return to normal. This provides an explanation of the value of hot moist applications to an inflamed part. The fomentations act through the local vasodilator nerves, increasing the hyperemia, hastening the formation of an exudate, and limiting the spread of the infection. It is possible that there may be a liberation of acetylcholine at the nerve endings, and that this may produce a local action on the vessels.

**Phagocytosis.**—A unicellular organism such as an amoeba shows to a marked degree the power of taking foreign particles into its body. The cell of which the organism is composed swallows or devours the particle. Hence the process is known as phagocytosis (*phagein*, to eat). The mechanism is that of amoeboid motion, the same by which the leucocytes pass through the vessel walls. The cytoplasm of the cell flows out in one or more processes or *pseudopodia*, which surround the particle and draw it within the body of the cell. Here it undergoes digestion, a vacuole being formed around it which contains a digestive ferment. If the particle can be dissolved and digested it gradually disappears; if not, it is discharged from the cell.

The power of phagocytosis is one of the fundamental properties of protoplasm. This is brilliantly demonstrated by the work of Metchnikoff, whose name will be forever associated with the process which he has traced through the lower members of the animal kingdom in his book on the Comparative Pathology of Inflammation. An excellent account of the historical development of the concept of phagocytosis is contained in Fried's paper. Phagocytosis is the means by which nourishment is taken into the body of the cell. It is therefore exhibited by a large variety of cells in the higher animals. Most highly developed in the wandering mesodermal cells, it is also seen in various epithelial cells, endothelial cells, and fixed connective tissue cells. Of the fixed cells, those which constitute the reticulo-endothelial system possess phagocytic powers in the highest degree. In the inflammatory exudate the group of large mononuclear cells known collectively as macrophages play the part of scavengers, removing dead leucocytes, erythrocytes, and tissue cells. A macrophage may contain half a dozen smaller cells within its cytoplasm. The name was used by Metchnikoff to distinguish it from the microphage or smaller phagocytic cell, in other words the polymorphonuclear leucocyte.

Phagocytosis, originally a means by which the cell absorbed nourishment, has been used by the body as an instrument in the removal of

irritants. When the unicellular stage of the protozoa is left behind it is found that the wandering mesodermal cells, which appear between the ectoderm and endoderm of multicellular animals, are *par excellence* the phagocytes of the body and therefore the body's defenders against irritation. In vertebrates these cells are represented by the polymorphonuclear leucocytes of the blood and the large mononuclear phagocytes of the blood and of the tissues, those cells called by Metchnikoff the macrophages. The former engulf bacteria, both alive and dead. If a mixture of leucocytes and bacteria is incubated and a film is then spread and stained, numbers of the bacteria will be seen lying within the leucocytes. (Fig. 37.) The macrophages devour dead cells, blood pigment, inorganic particles, etc. They are true scavengers. They may also engulf protozoal parasites.



FIG. 37.—Polymorphonuclear leucocyte containing bacteria.  $\times 1250$ .

In acute inflammation the polymorphonuclears play the chief part in the early stages, the macrophages taking their place in the later stages. The two sets of cells react differently to different bacteria. Thus the mononuclears will not take up streptococci or gonococci which the polymorphonuclears readily devour, but they will take up tubercle bacilli or leprosy bacilli.

The dependence of the health of the organism on the phagocytic power of its wandering mesodermal

cells is readily seen in the transparent body of the *Daphnia* or water-flea. When the *Daphnia* is invaded by some parasites, they are immediately attacked by the leucocytes and are soon killed. Other parasites excite no response from the leucocytes, so that they multiply until they fill the entire body of the *Daphnia* and bring about its destruction.

It becomes apparent that both in the lower and in the higher forms of life the most potent means of removing an irritant is the process of phagocytosis. In Metchnikoff's own words: "The *primum movens* of inflammation consists in a phagocytic reaction on the part of the animal organism. All the other phenomena are merely accessory to this process, and may be regarded as means to facilitate the access of phagocytes to the injured part." These views appear commonplace now, but they met with strong opposition at the time. One of the principal critics was Ziegler who wrote as follows: "I look upon the phagocytosis which occurs in an inflammation as a purely accidental phenomenon which is often brought about for the simple reason that mobile cells happen to be present, together with a material capable of being ingested by them."

When foreign particles which cannot be digested have to be removed,

such for instance as pieces of bone or cholesterol crystals, the macrophages fuse together so as to form *giant cells*. Such a foreign body giant cell is a cytoplasmic syncytium containing a large number of nuclei. In this form it seems to have greater phagocytic power than when the cells act singly. These cells are seen in various chronic inflammations such as tuberculosis and syphilis.

There is, however, another and more sinister side to phagocytosis. It has long been known that bacteria taken up by phagocytes may continue to live within the cells. An example of this is seen in the so-called lepra cells of leprosy, which are crowded with living leprosy bacilli. Goodpasture, using as his culture medium the chorio-allantoic membrane of the chick embryo, has shown that the initial stage of infection may be an invasion of the mesodermal cells (fixed or mobile) or epithelial cells, that the bacteria may proliferate within these cells, and that they may be carried by mobile cells to a distance. This initial intracellular proliferation seems to represent the first step in invasion in the case of many infections, and was observed with *Streptococcus viridans*, *B. typhosus*, *Br. abortus*, and *B. tuberculosis*, but not with *Streptococcus hemolyticus* and *Staphylococcus aureus*.

The cellular side of inflammation is not the only side, as Metchnikoff was apt to imagine. If leucocytes are washed free from blood plasma and are then mixed with bacteria, no phagocytosis will occur. Evidently some substances in the plasma are necessary for the reaction between leucocyte and bacterium to occur. These substances are called *opsonins*, and will be discussed further in the section on Immunity.

**The Mechanism of the Vascular Phenomena.**—The result of the vascular changes which have just been described is to bring both the solid and the fluid constituents of the blood from the interior to the exterior of the vessels, where they encounter the irritant responsible for the reaction. It has been said that the object of the exudate is to destroy and remove the irritant, and that the object of the vascular phenomena is the formation of the exudate. A teleological view of this kind is a mistake. There is nothing transcendental about the process, which is governed by purely physico-chemical laws and must not be looked upon as purposive in nature.

The varied changes of inflammation both in the vessel walls and in the blood and tissue cells are due to chemical stimuli produced at the site of irritation. The commonest of all irritants are bacteria, and these produce chemical substances which indirectly act upon the vessels. Even in aseptic inflammation caused by mechanical or thermal injuries there is destruction of tissue with the liberation of disintegration products which exert a similar action. An excellent account of the chemical side of inflammation will be found in Wells' *Chemical Pathology*.

The *vascular dilatation* which is so striking a feature is due to paralysis of the muscular fibers of the small arteries and veins. Krogh has shown that even the capillaries possess contractile power, and these

vessels also are paralyzed. It is probable that paralysis of the vaso-constrictor nerves may play a part in the earliest stage of inflammation, but as the vascular changes are seen in tissue which has been completely separated from the nervous system it is evident that the chief action is a direct one on the vessel wall.

Sir Thomas Lewis has shown that the vascular dilatation which follows firm stroking of the skin is due to the liberation of a histamine-like or "H"-substance. He suggests that in the tissue destruction of inflammation a similar substance is liberated and sets in motion the vascular mechanism. "The agent that alarms the garrison and mobilizes the first or vascular defenses is a chemical agent derived from the tissues. The perfection of this mechanism is such that the defense is organized immediately and at every threatened point; it is arranged and carried through locally, being independent of higher systems of control (nervous) and of distribution (cardiovascular)." (Lewis.)

The *slowing of the blood stream* may be attributed to three factors. Of these the most important is the increased peripheral resistance caused by the great swelling of the endothelial cells of the capillaries. This in turn is due to the action of metabolic acid products such as lactic acid, which by increasing the affinity of the cell protoplasm for water causes the cells to imbibe fluid and thus become swollen. The second factor is the greatly increased concentration of the blood due to the copious out-pouring of plasma into the tissues, rendering the blood more viscous. The third is the increased resistance to the flow caused by the accumulation of leucocytes along the inner surface of the veins.

The *escape of the blood plasma* is probably due to a number of factors. The capillary walls are injured by the toxins and are thus rendered more permeable. The osmotic pressure of the tissues is increased, due to the colloid proteins being broken down into crystalloid substances with a high osmotic pressure. This disturbance of the osmotic pressure causes the plasma to pass from the vessels into the tissues.

It is the *emigration of the leucocytes*, however, which has the greatest suggestion of purposiveness. They multiply in the bone-marrow and thus increase in number in the blood stream, they pass through the walls of the vessels and accumulate at the site of irritation, and they finally engulf and devour the bacteria by the process of phagocytosis to be described presently. These actions seem intelligent and volitional, but they can be explained on a physico-chemical basis. The force which not only draws the leucocytes out of the bloodvessels but causes them to move through the tissues is known as *chemotaxis*, and has been defined as "a directional response to a substance in the environment" (McCutcheon).

Menkin has shown that a crystalline nitrogenous substance can be obtained from acute inflammatory exudates which increases capillary permeability and induces prompt leucocytic migration. For this reason he calls the substance *leucotaxine*. It appears to be a polypeptide formed as the result of the breakdown of proteins. It bears no

relation to histamine or the H-substance of Lewis. Menkin has also isolated from exudates a leucocytosis-promoting factor capable of exciting leucocytosis when injected intravenously in normal animals, and a necrotizing substance (necrosin) which appears to be liberated from the injured cells.

The living amœba responds readily to chemical changes in its environment. When a little dilute acid is placed in the neighborhood of the amœba it will at once move towards it owing to the force of chemotaxis, which in turn acts by lowering the surface tension. Leucocytes behave in exactly the same way, and move towards bacterial toxins even though they are at once killed by the latter. When the toxins are freed from their microorganisms the result is the same. Heat of moderate degree attracts both leucocytes and amœba, a process known as thermotaxis. The most marked effect is obtained with temperatures approximating that of the body, 36° to 39° C. (97° to 102° F.). With higher temperatures the leucocytes cease to be attracted. These facts may be borne in mind when applying heat locally for therapeutic purposes.

There is a negative as well as a positive chemotaxis. Such substances as quinine, alcohol, and lactic acid repel rather than attract the leucocytes. The result depends to some extent on the concentration of the material. If the solution is made sufficiently dilute the negative action is changed into a positive one. When bacteria are extremely virulent they cease to exercise any positive chemotactic power, and merely paralyze the leucocytes. If the two ears of a rabbit are inoculated with an attenuated and a virulent culture respectively, in the former there will be a great accumulation of leucocytes with very little fluid, while in the latter there will be an abundant effusion of fluid but hardly any leucocytes.

The various leucocytes show different degrees of response to chemotaxis. The polymorphonuclear leucocytes are the most readily affected. The lymphocytes are much less active, probably because of the small amount of mobile cytoplasm which they contain. For this reason it seems likely that most of the cells of "small round cell" collections in chronic inflammation are derived from the tissues rather than from the blood. Of particular interest is the behavior of the white cells in an inflammatory focus in a patient with lymphatic leukemia. In this disease there may be 99 per cent of lymphocytes in the blood to 1 per cent of polymorphonuclears, and yet if an inflammatory blister of the skin is produced, the exudate consists of polymorphonuclear forms with hardly a single lymphocyte. The products of animal parasites attract the eosinophil leucocytes more than any other variety, so that these increase in number both in the blood and in the tissue affected.

It is possible that other factors besides chemotaxis play a part in the emigration of leucocytes. Clark and Clark studied the vascular endothelium microscopically in a transparent chamber in the rabbit's ear. In the early stages of inflammation individual leucocytes can be seen to stick at localized points of the vessel wall and then free them-

selves, due apparently to increased stickiness of the endothelium. Later the stage of stickiness is passed, and the endothelium separates into solid, hyaline globules.

Let us now apply these general considerations to a given instance of inflammation. Bacteria gain entrance to the finger and produce chemical poisons. Even if the irritant is non-bacterial the tissues are injured, and the chemical products of cellular disintegration are liberated. These chemical substances act upon the walls of the vessels producing the paralytic dilatation and the swelling of the endothelium already described. They pass through the walls of the capillaries at the thinnest parts, probably between the endothelial cells, and exert their chemotactic influence on the leucocytes flowing past. They lower the surface tension of the leucocytes on the side nearest the capillary wall, so that they move from the center of the stream over to the wall, to which they tend to adhere in a sticky manner. Still under the chemotactic influence, the leucocytes push out pseudopodia between the endothelial cells, and finally pass through the vessel wall. They then move through the tissue spaces to the site of the irritant. The chemotactic substances are carried by the blood stream to the bone-marrow, where they repeat the process on the leucocytes stored there, lowering their surface tension on one side and drawing them into the blood stream. In this way a leucocytosis is produced, the supply being kept up by proliferation of the parent cells of the leucocytes, the myelocytes of the marrow. As long as the blood contains more chemotactic substances than the marrow, the leucocytosis will increase.



FIG. 38.—Photograph of living leucocyte showing stretching of cytoplasm: (a) portion of leucocyte containing 3 red cells attached to slide; (b) migrating portion. (Mudd and Mudd, *Jour. Gen. Physiology*.)

Phagocytosis may be regarded as a special result of the process which has just been described. The leucocyte merely continues its onward movement until it flows around the particle and engulfs it. Stuart Mudd and his associates have shown that phagocytosis involves the spreading of the leucocyte over the surface of the particle until the latter is completely enclosed; the capacity of spreading is the



principal factor. (Fig. 38.) The deposition of serum protein on the surface of the particle greatly increases this power. When leucocytes are examined at the interface of an oil-water mixture, their remarkable deformity at once becomes evident. This appears to depend on the wetting properties of the leucocytes; they are hydrophilic. Red blood cells, on the other hand, are hydrophobic and exhibit no deformability. (Mudd and Mudd.)

This explanation appears to be the most reasonable which can be offered at the present time to explain the cellular phenomena of inflammation. As Wells remarks: "There seems to be no middle ground between such a physical theory and a metaphysical theory which would endow a single cell, without organs or nervous system, with the reasoning powers of highly developed animals, a position incompatible with the entire evidence of experience."

#### **The Inflammatory Exudate.—**

The exudate which collects at the site of irritation is partly derived from the blood (hematogenous), partly from the tissues (histogenous). The various forms of leucocytes of the blood migrate through the vessel walls; the blood plasma also passes out, and gives rise to the formation of fibrin; the wandering cells of the tissues accumulate at the site of irritation. These three constitute the inflammatory exudate. Red blood cells may be present in varying degree, but have no functional part to play. Let us now examine these various elements in greater detail.

#### **The Polymorphonuclear Leucocyte.**

—These cells are the active agents in acute inflammation, especially in its earlier stages. They are called forth in particular by the pyogenic group of bacteria, and form the chief constituent of pus. The ordinary pus cell is a polymorphonuclear leucocyte. The great increase in the number of leucocytes in the blood which occurs during inflammation is an increase of the polymorphonuclears. In sections of inflamed tissue the vessels may be packed with these leucocytes. They are attracted not only by bacteria but also by their toxins, as can be shown by the experimental injection of a toxin freed from the microorganisms by which it is produced.



FIG. 39.—Leucocytes collected at point of bifurcation of a dilated vessel.  $\times 200$ .

The cells collect in great numbers around the dilated vessels (Fig. 39), and they pass through the tissue spaces by their amoeboid movement. They are actively amoeboid and actively phagocytic. Their power of movement is remarkable, but they cannot swim through fluid with any degree of effectiveness. They must have a framework on which to crawl. It is fibrin which provides the interlacing pathways that bridge across the fluid-distended spaces on which the leucocytes can move. The phagocytic power is shown towards bacteria rather than to dead and disintegrating cells. They form the first line of defense of the body against pyogenic bacteria, and constitute the microphages of Metchnikoff. Having devoured the bacteria they secrete a digestive ferment which brings about solution of the bacterial bodies. Large numbers of the leucocytes are killed by the bacterial toxins, but even in their death they serve the body, for on disintegrating they liberate a proteolytic ferment which dissolves the dead tissue, and thus hastens the process of ultimate recovery. This ferment has a similar action on fibrin, and tends to prevent its formation. In a fresh exudate the cell outline is sharp and the nucleus distinct, but as degeneration proceeds the cytoplasm becomes granular, the outline indistinct, and the nucleus eventually disappears. Many of the cells which survive pass back into the lymphatics and bloodvessels and reënter the general circulation. The polymorphonuclears are unable to reproduce themselves, while the mononuclears have this power. This is one reason (albeit a teleological one) why the former migrate from the vessels in such large numbers, for the multiplication of the latter takes time. Menkin points out that the differential leucocyte picture in the exudate at a given time in the development of the inflammatory reaction is a function of the H-ion concentration of the exudate. An acute pleural exudate induced by a chemical irritant gradually develops an acidosis, and at the same time the polymorphonuclears are replaced by mononuclears. If, however, the alkalinity is maintained there is no change in the cell count. When the pH is alkaline the polymorphonuclears outnumber the mononuclears, when it is neutral the numbers are about equal, when it becomes acid the polymorphonuclears degenerate and give way to mononuclears. Polymorphonuclears are unable to survive as local acidosis increases.

**The Eosinophil Leucocyte.**—The eosinophils of the blood are few in number, constituting only from 2 to 4 per cent of the total white count. They appear early in the inflammatory exudate, and may disappear entirely from the blood. Their function is unknown, for they do not appear to be phagocytic. A marked increase in the number of eosinophils in the blood (eosinophilia) is characteristic of infection by many animal parasites. Large numbers of these cells are found in the tissue in which the parasite is lodged. In bronchial asthma the mucosa of the bronchi is often crowded with eosinophils. In both of these instances the eosinophilia may be a reaction against a foreign protein. A marked tissue eosinophilia is sometimes seen in appendicitis in the subacute or chronic stage. Eosinophils are frequently present in the

lesions in the lymph nodes in Hodgkin's disease. In these latter instances the cells may be derived from the tissues rather than from the blood.

**The Mast Cell.**—This is a cell with coarse basophilic granules in the cytoplasm, and an indented or polymorphonuclear nucleus. It is the basophil leucocyte of the blood, present normally in very small numbers, and is also found in the tissues. These cells are observed in mild subacute inflammations, but they show a marked tendency to disintegrate, so that the granules alone may be seen. Mast cell stain metachromatically with toluidin blue, and, as Jorpes has pointed out, tissues which are rich in heparin stain in a similar manner. Examples are the subintimal tissue of bloodvessels, and subpleural and subperitoneal connective tissue. It is reasonable to suggest that mast cells are concerned with the production of heparin.

**The Lymphocyte.**—In chronic inflammation and in the later stages of acute inflammation the lymphocyte may be the main cell of the exudate. The cells of such collections are often called by the non-committal name of "small round cells." Some of these cells no doubt are derived from the tissues, but for the most part they come from the blood. "The complete ignorance of the function of the lymphocyte is one of the most humiliating and disgraceful gaps of all medical knowledge. They phagocytose neither bacteria nor other particulate matter. Congregated often in the more peripheral parts of the lesion, they have the appearance of phlegmatic spectators passively watching the turbulent activities of the phagocytes" (Rich). It is now known that antibody formation occurs largely in lymph nodes (McMaster and Hudack), and there is evidence to suggest that the lymphocytes are the cells which produce the antibodies, although some workers believe that these cells merely store and carry the antibodies. Maximow believed that lymphocytes developed into macrophages, because in tissue culture he observed them acquiring a large amount of cytoplasm and the power of phagocytosis. Pathologists have not observed this transformation in tissue sections, but Kolouch has shown that it can occur rapidly. By injecting egg albumin into the subcutaneous tissue of rabbits and examining imprints of the exudate at short intervals he was able to demonstrate the hour by hour development of lymphocytes into phagocytic macrophages. The change was completed in less than eighteen hours. Kolouch's photomicrographs are very convincing. In chronic inflammation the lymphocytes remain for the most part as small round cells; in acute inflammation they appear to change into macrophages.

**The Plasma Cell.**—Two points regarding this cell are deserving of note. (1) It is never present in the normal blood, and (2) its form is so characteristic that it is readily recognized. (Fig. 40.) The plasma cell is larger than the lymphocyte with more abundant cytoplasm, it is not quite round but slightly polygonal in outline, and the nucleus is eccentric so that the cell has a lop-sided appearance. The chromatin is collected in small masses around the periphery of the nucleus like

the figures on a clock-face. The cytoplasm is basophilic, and it presents a clear area on the side of the nucleus which faces the center of the cell. It is probable but not certain that the plasma cell is a development from the lymphocyte. These cells are normally present in the intestinal mucous membrane. They may be extremely abundant in various tissues in chronic inflammation. The synovial membrane in chronic arthritis may be crowded with plasma cells. Inflammation of the Fallopian tubes offers a good example. It is usually present in syphilitic lesions. It is seen in the Aschoff nodules of rheumatic fever. The part which this cell plays in inflammation is not known with certainty. Probably it is the same as that of the lymphocyte.

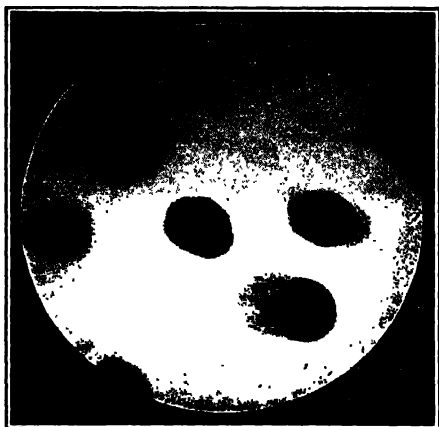


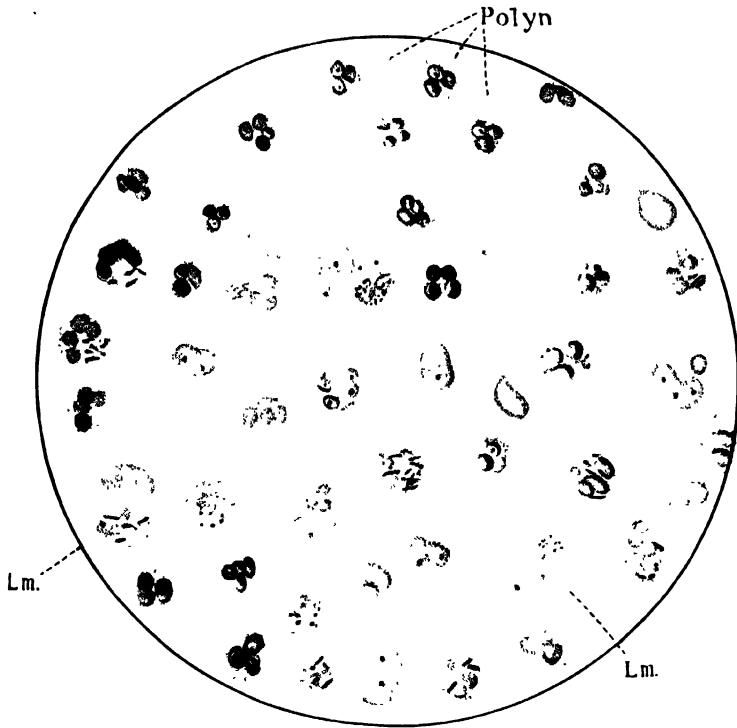
FIG. 40.—Two plasma cells showing polygonal shape and eccentricity of nucleus. The other two cells in the center are lymphocytes.  $\times 1600$ .

**The Macrophage.** — Many names have been given to the large mononucleated cells which play so important a part in the later stages of acute inflammation and in some types of chronic inflammation. Amongst such names may be mentioned polyblasts (Maximow), clasmatocytes (Ranvier), adventitial cells (Marchand), large mononuclears, monocytes, histiocytes (Aschoff), and macrophages (Metchnikoff). Some of these names reflect doubt as to their origin. It is probably two-fold: from the blood and from the tissues.

In the discussion on the lymphocyte it was pointed out that there is good reason to believe that many lymphocytes derived from the blood become converted into macrophages at the site of inflammation by increase in the cytoplasm and enlargement of the nucleus. Ebert and Florey, using Clark's transparent observation chamber in the rabbit's ear and moving picture technic, observed monocytes marked by vital dye and traced their passage through capillary walls into the tissues, where they became converted into macrophages.

It is probable that the bulk of the macrophages are histogenous in origin, particularly from the reticulo-endothelial system. They are derived not only from cells lining blood sinuses, such as the Kupffer cells of the liver, but from the tissue cells of that system known as histiocytes. In addition to the fixed cells there are nomadic mesodermal cells which have no fixed abode, but wander through the tissues by virtue of their amoeboid powers. The distinction between the fixed and the wandering cells can be most readily realized by studying tissue cultures, and can be demonstrated in a dramatic manner by projecting a moving picture of the culture on the screen, when the actively amœ-

PLATE III



Film Made from Peritoneal Fluid in Case of Peritonitis set up by Inoculating *B. Coli* Twenty-four Hours Previously into the Abdominal Cavity of a Rabbit. (Beattie.)

*Polyn* , Polynuclear leukocytes, many containing bacilli; *Lm.*, large hyaline mononuclear cells, many acting as phagocytes for polynuclear cells, red corpuscles, etc.



boid and actively phagocytic nature of these cells becomes vividly apparent.

MacCallum has given an unsurpassed description of such a picture. "The connective tissue cells grow out majestically and smoothly from the margin of the field, crossing and interlacing until a firm new structure is formed. Among these cells one may see others of quite different aspect worming their way with no thought of building. Arrived at the margin where they escape from the entanglement of these more serious fibroblasts, they show their true characters. Some are polymorphonuclear leucocytes, and they hop about within a limited area in a sort of ecstatic frenzy, evidently throwing out and retracting pseudopods at a great rate. Then there are lymphocytes which move humbly, like plugs crawling only a little way with head to the ground. But also there are macrophages which reach out great arms, perhaps in two or more directions, and at the end of these arms there is a flourish of clear protoplasm with outflung streamers that wave and search about for whatever can be seized, or else the whole advancing margin of the cell flows out and comes back like a wave, sucking in any particle that comes in its way." In the fixed and stained tissue of a microscopic preparation the cells lose all this vivid character, and appear as large pale rounded bodies with a vesicular nucleus and abundant cytoplasm.

Carrel and Ebeling found that some features of the macrophage in tissue culture can be best studied by means of dark-field illumination. They give a graphic account of what is seen in this way. The marginal portion or kinoplasm of the cell is an extremely thin membrane which is invisible when viewed by direct light but is readily seen in the dark field. It undulates incessantly like a delicate silk veil when blown by the wind, and it is from this structure that the pseudopods are formed. When the macrophage stops progressing and becomes circular the membrane unfolds and moves more rhythmically, like the waves of the sea on a sandy shore. Should a lymphocyte approach, it is rapidly enveloped by the foldings of the kinoplasm, and appears to glide into them toward the body of the macrophage, where it is finally digested. The kinoplasm appears to play the part of the spider's web.

It is these cells which form the scavenger cells of ordinary inflammation, the epithelioid cells of tuberculosis and syphilis, the compound granular corpuscles which surround an area of brain softening, the heart failure cells which take up blood pigment in the lung when the heart is failing, the large phagocytes which form a zone around a chronic abscess, and finally, when the utmost in phagocytic action is needed, they fuse together to form giant cells. Their amœboid and phagocytic character is better seen in smears made from inflammatory exudates and immediately fixed (Plate III) than in sections of inflamed tissue, in which the pseudopodia are retracted and the outline becomes rounded.

**Giant Cells.**—When the individual macrophages are unable to deal with particles to be removed, they fuse together and form multinu-

cleated giant cells. Excellent examples of giant cell formation can be seen around a foreign body such as a fragment of bone, a piece of ligature, a crystal of cholesterol, or even a splinter of wood. (Fig. 41.) For this reason the cells are called foreign body giant cells. They may contain enormous numbers of nuclei, which cannot all be seen in one section, since the cell is spherical. It is believed by some that these cells may be formed by amitotic division of the nucleus, the cell body remaining undivided. Comparative pathology lends little support for this view. In the transparent larvæ of the lower invertebrates the macrophages can be seen to cluster around a foreign body and fuse together into a multinucleated plasmodial mass which completely surrounds the intruder. Illustrations of this process may be seen in Metchnikoff's book. Another method of studying the question is by the use of tissue cultures. When mesodermal cells are grown in culture they can often be seen to fuse together and form multinucleated giant cells. At the same time the possibility that some giant cells are formed by amitotic division of the nucleus cannot be denied.

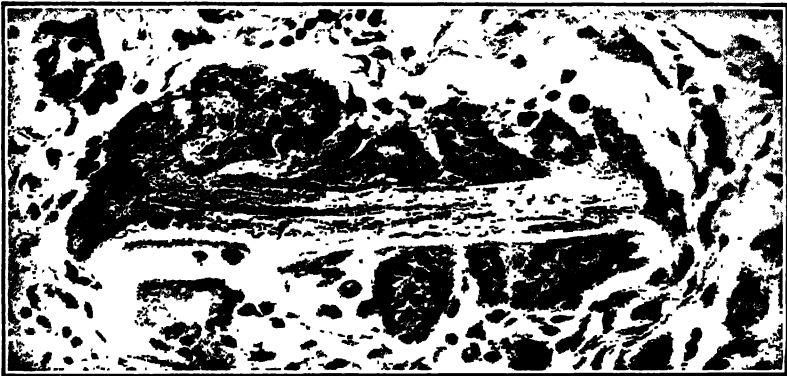


FIG. 41.—Sliver of wood surrounded by giant cells.  $\times 300$ .

It must not be supposed from this brief summary that the subject of giant-cell formation is as simple as it sounds. Haythorn's excellent review of the whole subject contains 391 references. Three great classes of giant cells must be distinguished: (1) tumor giant cells, (2) foreign body giant cells, (3) a miscellaneous group. (Figs. 42 and 43.)

*Tumor giant cells* are best seen in osteogenic sarcoma of bone, in gliomastoma multiforme (a malignant tumor of the neuroglia), in rhabdomyosarcoma (a malignant tumor of muscle), and in primary carcinoma of the liver. They are large cells, and have one or several nuclei, but these are never very numerous. The nuclei are often hyperchromatic so that they stain very darkly, and may vary considerably in size and shape, so that the cell has a more atypical neoplastic appearance than the Langhans' type of cell. The genesis is also different,



for tumor giant cells are formed by the nucleus of the cell dividing while the body of the cell fails to divide. These giant cells are not derived from the macrophages, but from the cells of the tumor, whether connective tissue or epithelial in nature.



FIG. 42

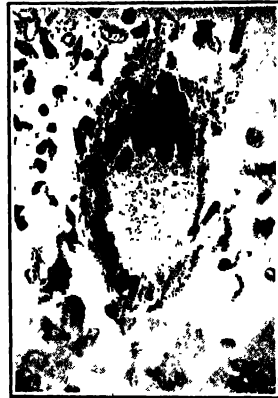


FIG. 43

FIGS. 42 and 43.—Types of giant cells.

FIG. 42.—Tumor giant cell with several large nuclei.  $\times 400$ .

FIG. 43. Foreign body giant cell with a large number of smaller nuclei arranged around the periphery and at one pole.  $\times 700$ .

The *foreign body giant cell* is larger than an ordinary cell and may be of enormous size; it contains numerous nuclei, sometimes as many as 50 or 100. The nuclei are regular in size and seldom large. In the ordinary type of giant cell engaged in removal of a foreign body, the nuclei are scattered through the cytoplasm. In the giant cells so characteristic of tuberculosis, also known as the Langhans' type of giant cell, the nuclei tend to be arranged around the periphery or are collected at one or both poles of the cell.

Foreign body giant cells may be found in a great variety of conditions. Of these the commonest is tuberculosis, but it is a great mistake to jump to the conclusion that a lesion containing giant cells must be tuberculous. They are found in other chronic destructive inflammations such as syphilis, leprosy, actinomycosis, and blastomycosis. In leprosy the cells may be crowded with bacilli (lepra cells), and in tuberculosis they may contain a smaller number of tubercle bacilli. Any destructive lesion of bone may contain giant cells. They form the most striking feature of the giant-cell tumor of bone. Giant cells may be found at the site of old hemorrhages, but they are more often associated with attempted removal of cholesterol crystals. I have seen examples of this in atheroma of the aorta. The lesions of traumatic fat necrosis often show numerous giant cells, and are easily mistaken for the lesions of tuberculosis.

In addition to the two great groups of tumor giant cells and foreign

body giant cells, a *third miscellaneous group* may be recognized. In certain conditions of continued irritation the mesodermal cells become larger and may contain several nuclei. The large Aschoff cells of the rheumatic nodule offer one example. Another is the Dorothy Reed cell of Hodgkin's disease.

**The Lymph of the Exudate.**—Under normal conditions a certain amount of blood plasma passes through the vessel walls into the tissue spaces where it constitutes the lymph. From these spaces it is absorbed into the lymphatics, and passes *via* the thoracic duct back into the blood stream. There is thus a continuous flow from the blood into the tissues, but the fluid is absorbed at an equal rate so that it does not accumulate in the tissue spaces.

The lymph which escapes from the vessels is not the same as the plasma which remains; it is thinner and contains much less protein, owing to the selective action of the vascular endothelium.

In inflammation the outward flow is enormously increased. By inserting a cannula into one of the chief lymphatics of the leg and then producing inflammation of the foot by immersing it in hot water, Cohnheim was able to show that the flow of lymph might be increased to eight times the normal. Drinker and his associates have recently amplified these observations. They found that the lymph flow in the inflamed part showed an extraordinary increase, and that the subcutaneous lymphatics were so greatly dilated that they could be injected with ease. It is evident that the lymphatics do not collapse as the result of pressure of the fluid in the tissues, as is sometimes supposed. The normal lymph pressure in the leg of a dog is too low to be measured, but in sterile inflammation it rose to 120 cm. of lymph. The increased lymph flow lasted as long as twenty-four hours. The production of fluid is so great that it cannot be carried away by the lymphatics, and therefore accumulates in the tissue spaces. Here it gives rise to inflammatory edema, which is the chief cause of the swelling of the part in acute inflammation. The lymphatic channels tend to become blocked with the inflammatory products; this increases the accumulation in the tissues. Inflammation of the lymphatics (lymphangitis) will still further aggravate the condition.

The principal factors in the production of inflammatory edema are changes in the capillary wall and increased osmotic pressure in the tissues.

The dispute regarding the filtration and secretion theories of the production of lymph must be left to the physiologists. We may take refuge in that non-committal term, the *permeability of the capillaries*. This is greatly increased by the action of the products of irritation on the vascular endothelium, so that the plasma is no longer held back within the vessels. Not only is the amount of lymph which escapes greatly increased; its quality is also changed. Normal lymph usually contains less than 1 per cent of protein, whereas in inflammation the lymph may contain as much as 8 per cent.

Of much greater importance is the *increased osmotic pressure* of the

tissue fluids at the site of inflammation, which is a far more powerful force than the pressure inside the vessels. Early in the inflammatory process as the result of tissue disintegration metabolic products are liberated, for the most part acid in reaction, and these so raise the osmotic pressure that fluid is drawn from the vessels to dilute them.



FIG. 44.—Muscle fibers of appendix widely separated by fluid exudate.  $\times 200$ .

The *amount* of the fluid exudate varies greatly, depending on two main factors, the irritant and the site. (1) The bite of a mosquito and the sting of a nettle are examples of irritants which cause a marked outpouring of fluid. In a blister the exudate is almost entirely serous. Influenzal pneumonia is characterized by an extreme degree of inflammatory edema in the pulmonary alveoli. (2) The more open the tissue, the greater will be the exudate. It is most marked in serous sacs (pleurisy, peritonitis). In loose cellular tissues the fluid may be abundant. It may separate the muscle fibers of the appendix in acute appendicitis. (Fig. 44.) In such dense structures as bone the amount is negligible.

*Fibrin formation* is intimately associated with the inflammatory lymph. The fibrinogen of the plasma passes out with the lymph, and this is acted on by the thrombin liberated by the disintegration of the polymorphonuclear leucocytes with the production of fibrin. This takes the form of a series of fine threads interlacing with one another. (Fig. 45.) The amount of fibrin varies with the irritant and the location, just as does the amount of lymph. Some bacteria such as the pneumococcus and the diphtheria bacillus excite an abundant formation of fibrin. Much fibrin is formed on serous surfaces such as

the pleura and the peritoneum. Proteolytic ferments liberated by the leucocytes tend to prevent its formation, so that in an abscess crowded with pus cells no fibrin will be formed. The fibrin plays an important part in the process of healing, acting as a temporary scaffold on which the new tissue is built up. It may serve as a barrier against spread of the infection, so that in pneumonia the pneumococci do not readily pass from the lung into the pleural cavity. As an offset to these advantages is the fact that adhesions take their origin in the fibrin. Such adhesions are of value at first for they serve to localize the inflammation as in the case of an inflamed appendix. Later they may exact a penalty by undergoing contraction and thus gravely interfering with the function of the part affected.

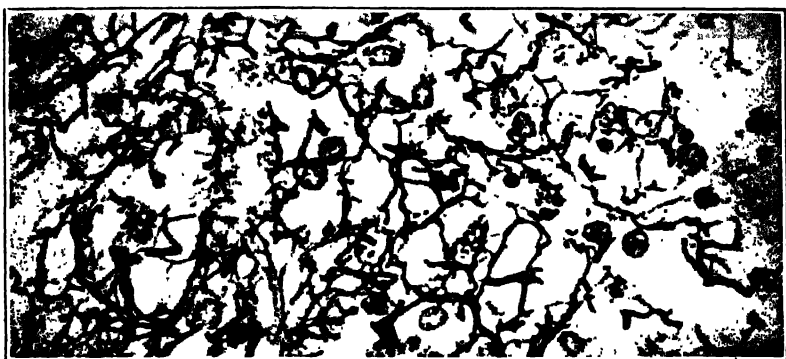


FIG. 45.—Exudate consisting mainly of fibrin.  $\times 600$ .

**Relation of the Lesions to the Cardinal Signs.**—It now becomes a simple matter to picture the pathological basis of the cardinal signs of inflammation. The *heat* is due to the increased amount of blood flowing through the part. The *redness* is also caused by the local hyperemia. The *swelling* is to be attributed in part to the vascular dilatation, but much more to the accumulation of exudate in the tissues. The chief constituent of the exudate responsible for the swelling is the lymph, the accumulation of which leads to inflammatory edema. There may be marked enlargement of an inflamed appendix, even though the cellular exudate is slight. The *pain* is caused by pressure on nerve endings. If the tension is great, as in a dense structure like bone, the pain will be severe. Stretching of a serous membrane rich in nerves will also cause much pain. *Loss of function*, varying in degree, is partly due to pain, partly to destruction of tissue.

**The Tissue Changes in Inflammation.**—The vascular phenomena and the formation of an exudate do not constitute the whole pathology of inflammation. There are also tissue changes. These may be of two types, (1) degenerative and (2) proliferative. If the irritant is intense, the effect is degeneration and destruction. If it is mild it

acts as a stimulant, and the effect is proliferation. Growth will either be impaired or enhanced, the result depending on the intensity of the irritant. At the center of the inflammatory area the action of the irritant is severe, so that degeneration predominates; at the periphery the action is mild, so that the tissue may be stimulated to proliferate. This part of the inflammatory process is known as repair or healing.

The bacterial toxins poison the tissues of the inflamed part, leading either to degeneration or death (*necrosis*). Both of these processes have been discussed in the chapter on Degenerations. The two most common degenerations are *albuminous degeneration* or cloudy swelling and *fatty degeneration*. If either of these is carried too far the affected tissue will die and become necrosed. Should thrombosis of the vessels occur, necrosis will be hastened, as the tissues have lost their food supply. In addition to the bacterial toxins, the proteolytic ferments liberated by the broken-down leucocytes play an important part in the destructive processes, although they are unable to act on living cells. These ferments produce liquefaction of the dead tissues. The result is the formation of the fluid known as *pus*. It must not be supposed that every inflammation goes on to the formation of pus, and so becomes *purulent* in type. Some bacteria are pyogenic or pus-producing. Most of the pathogenic cocci are in this class and many bacilli. But some bacilli, such as the tubercle bacillus, lead to a proliferative reaction with little or no attempt at pus formation. Even the pyogenic cocci when few in number or of mild virulence may fail to produce a purulent inflammation. Large numbers of leucocytes are necessary for the formation of pus. If the exudate consists mainly of lymph or of fibrin, not sufficient leucocytes are present to produce the liquefaction which is necessary for pus formation. The serum contains an antibody which tends to inhibit the proteolytic enzyme of the leucocytes, so that in serous exudates there will be no autolysis. The leucocytes of some animals, such as the rabbit, contain but little enzyme; such animals usually fail to produce liquid pus. Living cells are not affected by digestive enzymes. Thus in lobar pneumonia the dead cells of the exudate undergo autolysis (resolution), but the living walls of the alveoli are left intact.

**Inflammation of Serous Membranes.**—Inflammation of the pericardium, pleura, peritoneum, etc., is usually serofibrinous in type, *i. e.*, the exudate in the cavity is serous, but fibrin produced by coagulation of the exudate is laid down on the smooth surface of the membrane, covering it with a sticky shaggy exudate or in milder cases merely robbing it of its normal sheen and imparting to it a frosted or ground-glass appearance. Microscopically the exudate consists mainly of fibrin, with a varying number of polymorphonuclears and some serum. As a result of the relative absence of pus cells from which the proteolytic ferments of inflammation are derived, the fibrinous exudate is not removed by autolysis. Instead, it undergoes the process known as *organization* which will be studied in connection with repair. New fibroblasts grow into the exudate and remove it in part or whole. If

some of the exudate remains it is converted into dense fibrous tissue. If the two serous surfaces are stuck together by the exudate, as is often the case, the invasion of fibroblasts will sew the surfaces together at this point with permanent *adhesions*.

**Suppuration.**—If the dead tissue in an inflamed area undergoes softening and liquefaction the process is known as suppuration and the fluid formed is pus. This is the method by which the dead material is removed from the body. There are three requisites for suppuration: (1) necrosis; (2) the presence of sufficient leucocytes; (3) digestion of the dead material by proteolytic ferments. If any one of these is absent suppuration will not occur. Anything which will produce both positive chemotaxis and necrosis will produce suppuration. Not only pyogenic bacteria and their toxins, but aseptic irritants such as turpentine and croton oil will cause typical suppuration. *The presence of leucocytes does not constitute suppuration.* The tissues may be crowded with polymorphonuclear leucocytes, but suppuration and pus formation need not be present. (Fig. 46.)



FIG. 46.—Muscle fibers of appendix separated by leucocytes but without suppuration.  
× 500.

The digestive ferments are produced mainly by the leucocytes, and to a lesser extent by the necrosed tissue cells and the infecting bacteria. The part played by the leucocytes is readily shown by testing the action of pus on fibrin or egg albumen. This is easily dissolved by pus or purulent sputum, whereas non-purulent sputum has no effect. The action of the protease of the leucocytes tends to be inhibited

by the antienzymes of the serum. On this account, if the exudate be rich in serum and poor in leucocytes, no liquefaction and suppuration will occur. Drainage of the serum by removal of the antienzymes may lead to liquefaction and removal of the dead tissue. In some animals such as the rabbit the leucocytes are poor in protease and the serum is rich in antienzymes. Opie has shown that in such an animal infection with the ordinary pyogenic cocci does not result in the formation of pus. The antienzymes appear to be of lipoid character, such as unsaturated fatty acids. Tuberculous caseous material is rich in unsaturated fatty acids and therefore resists liquefaction. The toxins of the tubercle bacillus appear also to destroy the autolytic ferments. Another reason why the ordinary tuberculous lesion does not suppurate is that it does not contain leucocytes. If secondary infection occurs, or even if leucocytes are attracted to the part by the injection of iodoform, liquefaction and suppuration will soon follow.

The reaction of the inflammatory exudate bears a relation to the cytological picture (Menkin). The H-ion concentration increases as inflammation proceeds, due to the increased glycolysis, and there is a gradual shift from polymorphonuclears to mononuclears. When the pH drops below 6.5 most of the leucocytes are injured and frank suppuration develops.

*Pus* is the fluid product of suppuration. It is alkaline in reaction and usually yellowish in color. It consists of pus cells and pus serum, but in addition it contains the debris of tissue destruction and bacteria living or dead. The pus cells are leucocytes, for the most part polymorphonuclear in type. If the exudate is fresh as in the discharge from a recent gonorrhea, the details are sharp and the cells are well preserved. If the exudate is old, all details may be lost.

The *pus serum* is inflammatory lymph to which are added the products of cell disintegration. It does not coagulate, because the fibrinogen of the blood plasma is destroyed by the enzymes of the leucocytes. It is for this reason that the exudate of a serous pleurisy when removed from the body will clot into a jelly-like mass, while the much thicker exudate of a purulent pleurisy (empyema) will remain uncoagulated. Pus serum contains a large amount of nucleoprotein, which is insoluble in acetic acid, as well as fats and lipoids (cholesterol), derived from the broken-down cells. Albumoses in the pus are absorbed into the blood, and are often excreted in the urine, a condition of albumosuria.

An *abscess* is an example of localized suppuration. The inflammation is limited to one area, and as the irritant is a pyogenic one, pus is produced. When staphylococci lodge in the kidney, an acute inflammatory reaction results, the cells in the center of the focus are killed, and are liquefied by the proteolytic enzymes. (Fig. 47.) In this way a cavity is produced which contains fluid pus. The wall of the abscess cavity consists of damaged but still living tissues. It is here that the struggle goes on to limit the spread of the infection. (Fig. 48.) This limiting zone is crowded with polymorphonuclear leucocytes and

with macrophages filled with débris. Pus cells are continually discharged from this zone into the abscess, so that it is called the *pyogenic membrane*. If the abscess is chronic, or if the infection is dying out, the macrophages will greatly out-number the polymorphonuclears. Further out the tissue becomes more normal.

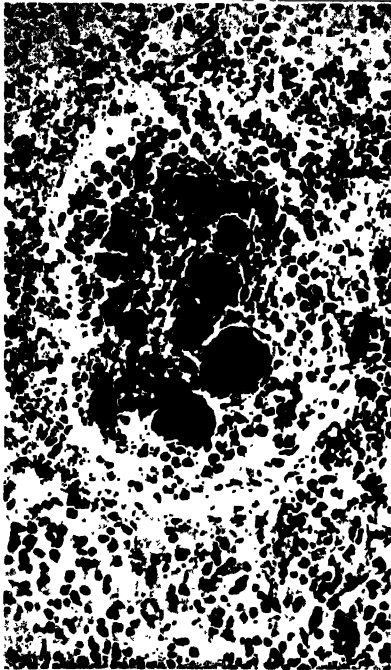


FIG. 47.—Abscess of kidney showing dark masses of bacteria and destruction of tissue.  $\times 275$ .

If the infection continues active, more and more material is added to the abscess, so that the pressure within it rises. It therefore tends to extend or “point” in the direction of least resistance. In the kidney it may discharge into the renal pelvis or on to the surface of the kidney. If the abscess enters a muscle sheath such as that of the *psoas* it may trek along it for a considerable distance.

The path formed by an abscess in its effort to discharge on a free surface is known as a *sinus*. Should the abscess discharge simultaneously on to both a skin and a mucous surface, the path which connects these surfaces is called a *fistula*. If the mucous surface is in the bowel, feces will be discharged on the skin, and the fistula is a *fecal fistula*. A good example is the abscess which may form when an inflamed appendix ruptures, and which may eventually discharge both into

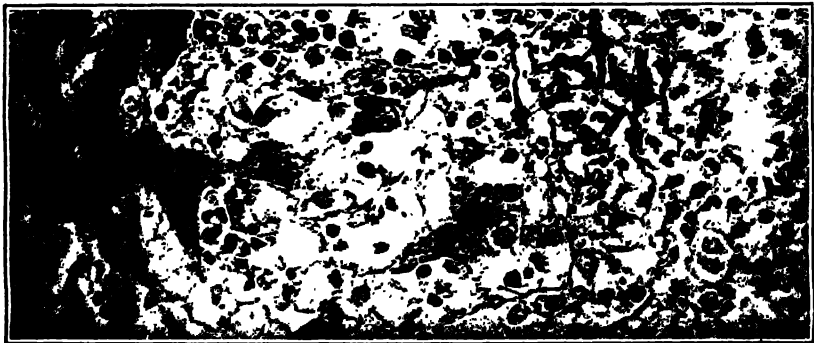


FIG. 48.—Wall of abscess in liver. At the left the liver cells are comparatively uninjured. At the right there is an acute inflammatory exudate.  $\times 300$ .



the bowel and on to the abdominal wall. When an abscess reaches a surface, either skin or mucous membrane, the overlying tissue becomes necrosed, forming a *slough*, and when the slough is discharged an open sore or *ulcer* is produced. This is the usual fate of an abscess. An ulcer, which is an open sore, an interruption of surface continuity of skin or mucous membrane with accompanying inflammation, is, of course, frequently produced by injurious agents acting directly on the surface.

An acute inflammatory lesion which discharges on the surface generally heals quickly. Such a healing ulcer is called a *healthy ulcer*. Its floor is covered by pink granulations composed of the vascular connective tissue known as *granulation tissue*, any discharge which comes from it is slight and contains only a few pus cells, the edges are sloping and are bordered by a bluish-white line of ingrowing epithelium, and the surrounding parts are not inflamed. An ulcer may fail to heal and be *unhealthy* because of continued infection or defective circulation in the part. In such an ulcer the base is bathed with pus, the edges are ragged owing to continued tissue destruction, the epithelium shows no sign of covering the ulcer, the surrounding parts are inflamed and edematous or may be hard and sclerotic from fibroblastic proliferation. (Fig. 49.)

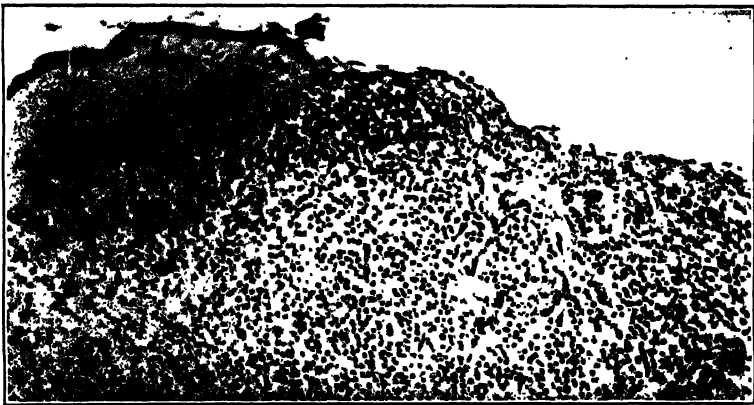


FIG. 49.—Non-healing ulcer. The epithelium on the left shows no sign of growing over the inflamed floor of the ulcer.  $\times 125$ .

If the infection is mild or is overcome by the defense reaction, the necrotic tissue becomes separated from the living tissue, partly because of liquefaction, partly owing to the phagocytic activity of the macrophages. A small abscess may be shut off in this way from the surrounding tissue, and the walling off is intensified by proliferation of fibroblasts and the formation of a limiting zone of fibrous tissue.

A *boil* is an abscess of a hair follicle or a sebaceous gland, caused by the *Staphylococcus aureus* which has penetrated the opening of a duct, owing it may be to repeated friction, so that it is commonest on

the buttocks or the back of the neck. There is marked fibroblastic proliferation, which, with intercellular formation of fibrin, causes the characteristic induration. The tension thus becomes high and is responsible for the pain. There may be very little liquefaction of the necrosed tissue, so that the center of the boil is composed of a solid "core" instead of pus. In a *carbuncle* the infection spreads to the subcutaneous tissue where it causes a more diffuse lesion which discharges on the surface by a series of openings, and from which toxic absorption is more liable to occur. The pus serum is absorbed into the lymphatics, the pus becomes inspissated, and the dead tissue is converted into a mass of fatty débris in which lime salts may be deposited. This fatty change with calcification is seen much more commonly in tuberculous lesions than in acute inflammation.

The reverse side of the picture is presented by those cases where on account of the intensity of the irritant and also because of widespread thrombosis there is not only necrosis of the surrounding cells, but death of the entire part. This is called *gangrene*. In this way a part or the whole of the appendix may die and become gangrenous.

So far we have only considered suppuration limited to a circumscribed area. The suppuration may spread through the tissues, a condition known as *cellulitis*. Streptococci are more likely to cause a spreading inflammation, staphylococci a limited one. This difference depends in part on the intensity of the local inflammatory reaction; this is much more severe in staphylococcal than in streptococcal infections. Menkin claims that this is on account of blocking of the lymph channels by fibrin. Staphylococci produce a clotting principle or staphylocoagulase which favors fibrin formation, whereas streptococci produce a fibrinolytic principle which breaks down and prevents the formation of fibrin. For these reasons the constitutional reaction (due to widespread bacterial invasion) may be in inverse proportion to the intensity of the local reaction.

**Relation of Tissue Response to Type of Infection.**—It must not be thought that inflammation is a stereotyped series of changes which follow upon any infection of the tissues. The reverse is the case. The reaction to different irritants is very varied. Kettle has pointed out that the tissue response is often so characteristic that the type of infection may be deduced from the histological picture. Some bacteria show a predilection for certain tissues. The meningococcus usually attacks the meninges, the diphtheria bacillus the throat, the influenza bacillus the bronchial tree, the pneumococcus the lung, the gonococcus the urethra, the typhoid bacillus the lymphoid tissue of the bowel, the dysentery bacillus the intestinal mucous membrane.

The histological picture may be so characteristic that a definite diagnosis of the infecting microorganism can often be made, even though it cannot be demonstrated in the tissues. The *staphylococcus* and the *streptococcus* are both pyogenic or pus-forming organisms, but the staphylococcus attacks skin and bone and gives rise to localized lesions with dense collections of leucocytes and abscess formation,

whereas the streptococcus often attacks mucous membranes, the exudate is more fluid, the lesion less localized, and the infection spreads widely through the lymph spaces of the tissues. In *pneumococcal* infections there is an abundant fluid exudate rich in coagulable protein, so that a large amount of fibrin is formed. In *anthrax*, on the other hand, there is an abundant fluid exudate which does not coagulate, so that blisters are formed. The peculiarity of *meningococcal* and *gonococcal* infections is the extreme degree of phagocytosis; in the early stages practically all the bacteria are intracellular. In spite of this marked phagocytosis the organisms are not killed, and probably multiply inside the leucocytes, which may thus serve to spread the infection. In the inflammation of *diphtheria* there is intense necrosis combined with an abundant outpouring of coagulable fluid, so that the resulting fibrin binds the necrotic material together to form a false membrane. Leucocytes are present at first, but undergo necrosis and disappear. The inflammation of *typhoid* infection is very characteristic, for it is confined to lymphadenoid tissue, and although the infection is an acute one the inflammatory cells are mononuclear in type with complete absence of polymorphonuclears; the bacilli invade the blood stream. The *dysentery bacillus*, which so closely resembles the typhoid bacillus both morphologically and culturally, produces an entirely different reaction. It attacks the intestinal mucous membrane, polymorphonuclears are abundant, a necrotic diphtheritic membrane is formed, and there is no blood invasion. The histological response in *rheumatic fever* is the very characteristic Aschoff nodule, composed mainly of mononuclear and multinucleated histiocytes.

In *tuberculosis* the lesion is a productive or proliferative one, with the formation of a tubercle composed of mononuclear epithelioid cells and occasional giant cells. The response to infection by the *Spirochæta pallida* is very similar. *Actinomycosis* also belongs to the group of the infective granulomata, but the tissue response to the streptothrix shows important differences from that of tuberculosis and syphilis. The fungus causes necrosis and an abundant exudation of polymorphonuclear leucocytes, so that an abscess is formed which is surrounded by granulation tissue and further out by dense fibrous tissue. In addition to this acute reaction there are epithelioid cells and a very occasional giant cell. The anaerobic group of bacilli which produce *gas gangrene* gives rise to still another type of reaction. There is an extreme degree of necrosis, liquefaction of the necrotic material, and gas formation, but complete absence of an inflammatory reaction.

**Varieties of Inflammation.**—A multitude of descriptive names have been applied to the various forms of inflammation. The meaning of most of these is self-evident, so that they need only be mentioned. An understanding of the principles which underlie the variations is far more important than any string of names. *Serous* inflammation is characterized by an exudate composed chiefly of serum. Pleurisy with effusion is an example. In *fibrinous* inflammation the chief element is fibrin. It is seen in dry pleurisy, in diphtheria, and in pneu-

monia. *Purulent* inflammation is suppuration. *Catarrhal* inflammation is a mild inflammation of a mucous membrane; the mucous cells pour out mucus with which are mingled desquamated epithelial cells and a certain number of leucocytes, but the process stops short of suppuration. A cold in the head is an example. *Membranous* or *diphtheritic* inflammation is a condition where the cells of a mucous surface are killed, an exudate is laid down on the surface, and the whole necrotic layer is bound by fibrin to the underlying tissue to form a "false membrane."

**Allergic Inflammation.**—When an animal or person is sensitized to bacteria by previous inoculation (*i. e.*, is in a state of allergy), a subsequent injection of the same organisms will cause a violent local reaction with inflammatory changes which are much more extreme than in the normal animal. This condition may be called allergic inflammation. Its two main features are: (1) the large amount of exudate and the tendency to necrosis and destruction of tissue, owing to the union of antigen and antibody within the cells; (2) the increased phagocytic power of the leucocytes and macrophages, as a result of which the infection is more readily overcome. In the chapter on Immunity we shall have occasion to observe that only the first of these features is a manifestation of allergy, the second being dependent on the acquired immunity which accompanies the allergic state. If the condition is of benefit to the animal it is on account of the second, not the first, of these features.

**Chronic Inflammation.**—When an irritant of low-grade intensity acts upon the tissues the result is said to be chronic inflammation, because it does not run the rapid acute course characteristic of acute inflammation. The tissue reaction is quite different from that of the acute form. It is often said to be productive in character, but the cells which collect in response to the irritation either come from the blood stream (lymphocytes, etc.), or are derived from those wandering tissue cells which go by the alternative names of histiocytes, mononuclears and macrophages. The only cells which proliferate are the fibroblasts.

The *infectious granulomas* form a special group. The most important member of the group is tuberculosis, but it also includes syphilis, leprosy, and the mycoses which are caused by fungus infection. In its original sense the lesion was a mass made up of granulation tissue, but it has come to signify an infective condition in which histiocytes are the principal cells, although lymphocytes, and plasma cells often play an important part. The histiocytes may become swollen, often containing lipid material in tuberculosis; such swollen cells are referred to as *epithelioid cells*. These may fuse together to form the *giant cells* which are characteristic not only of all the chronic granulomata, but also of the inflammatory reaction produced by a foreign body. The accumulation of cells may be so great that the lesion may form a tumor-like swelling; this is the reason for the misleading term *productive inflammation*.

In an organ such as the liver or kidney an intense irritant producing acute inflammation will destroy both the highly specialized parenchymatous cells and the more lowly developed connective tissue. An irritant of low intensity may kill the special cells, but only stimulate the fibrous tissue to proliferate, just as a degree of cold which will kill a race horse may merely stimulate a cart horse. John McCrae compares the parenchymatous cell to the professional man in a community, specially trained, not prone to be physically hard, nor over-given to reproduction. The supporting cell is its laboring-class brother, physically strong, not readily injured, but ready in reproduction. Chronic hepatitis (cirrhosis of the liver) and chronic nephritis afford examples of this truth.

The proliferating cells are in the main fibroblasts. The result may be a cellular fibrous tissue, or the fibroblasts may be stimulated to lay down collagen fibers rather than to multiply, with the result that dense acellular connective tissue is formed. Whichever course is followed it is evident that fibrosis will be one of the chief results of chronic inflammation.

It is customary to divide fibrosis into two great groups. The first is *productive fibrosis* due to the stimulating effect of the irritant or of the metabolic products of disintegrating cells on the fibroblasts. The second is called *replacement fibrosis*, in which fibrous tissue proliferates and replaces tissue which has been destroyed. This destruction may not be the result of inflammation, but may be due to a gradual cutting off of the blood supply to the part. A good example is the disappearance of myocardial fibers and their replacement by connective tissue as the result of gradual narrowing of the coronary arteries. Nevertheless it is evident from what has just been said that here also the connective-tissue cells may be stimulated by the disintegration products of the dying muscle fibers. Or we may put it more safely though more vaguely by saying that the dead tissue acts as an irritant to the surviving connective tissue. It is probable that some chronic inflammation for which no bacterial cause can be found is due to the presence of altered and broken down collagen, for when collagen is implanted in the tissues of an animal it produces a granulomatous reaction (Pullinger and Pirie).

A chronic inflammatory lesion is cellular at first, but becomes more and more fibrous as the irritation subsides and collagen is laid down. It follows the usual course of healing. But it is obvious from the nature of the process that the resulting fibrosis is likely to be much more marked than in acute inflammation. Newly-formed fibrous tissue invariably contracts as it becomes older, so that the affected organ will be shrunken as well as hard. Examples of these changes are healed tuberculosis of the lung and cirrhosis of the liver.

One word regarding nomenclature. A healed inflammatory lesion is not an example of chronic inflammation. It is not an "itis," so that when the surgeon finds a firm and shrunken appendix it does not follow that the patient is suffering from chronic appendicitis. The

appendix may be chronically inflamed, or it may be merely a fibrosed appendix; microscopic examination is necessary to settle the question. This subject is brought up because of a loose habit, all too common, of speaking of chronic appendicitis, chronic myocarditis, or chronic pleurisy when the speaker really means a fibrosed appendix, myocardium, or pleura.

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## CHAPTER V

### REPAIR

THE repair of injured tissue is as fundamental a process as inflammation. It is seen throughout the animal and vegetable kingdom. The lower in the scale the animal, the more complete is the regeneration. When the head of the earthworm is severed, a new one is formed, and this process can be repeated many times. The process of repair is so commonplace that we seldom pause to enquire what induces cells which have remained dormant for years suddenly to take on active growth. When looked at closely this is seen to be a remarkable phenomenon. Incise the most quiescent of fibrous tissue, and in twenty-four hours the connective-tissue cells have developed from mere nuclei into actively dividing fibroblasts. What is the cause of this sudden transformation? What is the *vis medicatrix naturæ*, the healing power of Nature?

It seems likely that the cells proliferate because they are stimulated. The stimulus is almost certainly chemical in nature. This chemical substance appears to be liberated by the degenerating cells. Carrel has shown that if in an aseptic wound all débris and blood clots are removed and the wound is completely protected from outside irritation no healing will occur. Even at the end of three weeks no change has occurred. But when the wound was covered with a slightly irritating dressing such as dry gauze or a weak turpentine dressing or when a few staphylococci were introduced, cicatrization commenced in less than two days.

The power of true repair, that is to say of replacement of destroyed tissue by the same type of tissue, varies with different organs. Some cells have developed to a stage at which it is impossible for them to proliferate, *e. g.*, nerve cells. When such cells are destroyed by injury or infection, as in infantile paralysis, it is impossible for them to be replaced by neighboring cells; "the moving finger writes, and, having writ, moves on." Liver cells have remarkable power of regeneration. So has surface epithelium. Connective tissue is the best example of perfect regeneration.

It is difficult to draw a hard and fast line between repair and inflammation. Both represent the reaction of the tissues to an irritant. Repair usually follows inflammation, and is usually preceded by it, but not always so. An irritant of some intensity produces inflammation and death of the tissues. At a distance the action is weakened, and the irritant becomes a stimulant, so that the tissue response now is proliferation. In this way reparative processes may go on at the same time as inflammation.

The most interesting modern observations on repair are those of Clark and his associates. By inserting a double-walled transparent chamber constructed of celluloid in a rabbit's ear they have been able to watch under the microscope the injured tissues recovering from the blow and setting themselves to reconstruct the part. They have even taken moving-picture microphotographs of the process. By this means new vessels can be seen differentiating and beginning to contract and dilate. Using intravital injections of methylene blue they could demonstrate the development of non-medullated nerve fibers going to the arteries; only when the vessels were supplied with nerves were they capable of contraction. The ingrowth of capillaries is followed by a remodelling of the indifferent plexus of vessels into an adult pattern, and a change into definite arteries and veins. The same is true of lymphatics, which also grow by sprouting, and appear later than the bloodvessels. Even the different stages of mitosis were seen and photographed. After injury associated with edema definite holes could be seen in the lymphatics which remained open for several days, allowing free passage of fluid and red blood cells into the injured lymphatics. This passage was not observed when the ear was splinted, thus demonstrating the importance of immobilization in the treatment of localized injuries and infections in order to prevent the entrance of bacteria into the lymphatics.

One of the most important elements concerned with repair is connective tissue. This is particularly true of repair of wounds. The formation of collagen satisfactory in quantity and quality is dependent on an adequate supply of vitamin C. Scurvy which is due to lack of vitamin C, is characterized by atrophy of connective tissue fibers, and under scorbutic conditions fibroblasts produce little collagen, and what is produced is of poor quality. It is evident, therefore, that an adequate supply of vitamin C is necessary for good healing. It has been shown clinically that when the vitamin supply is insufficient the healing of wounds is delayed and they tend to break open again (Crandon, Lund and Dill).

Repair is a wide process. It is seen in the healing of wounds. Exactly the same changes are observed in organization of an inflammatory exudate or a blood clot. The regeneration or replacement of any destroyed or degenerated tissue is another example of the same process. All of these must now be considered in greater detail.

**Repair in a Wound.**—The process of healing is fundamentally the same in all wounds, but there are marked quantitative differences, depending on the amount of tissue destruction and to a certain extent on the presence of sepsis. It is convenient to consider two very different types of wound.

**Healing of a Clean Incised Wound.**—This form of repair is still known by the old clinical name of "healing by first intention." A much better term is "primary union," the cut surfaces being brought together by stitches, so that the process is direct, with no intermediary substance playing a part. There is no appreciable loss of substance,



bleeding is at a minimum, infection is absent, and if the edges are brought into apposition there is hardly any exudate between the surfaces. The knife acts as an irritant, so that the edges will show slight inflammatory changes in the shape of vascular dilatation and exudation, and a small quantity of plasma, fibrin, and leucocytes will be present in the thin gap. Although the wound is strictly *aseptic*, it is not bacteriologically *sterile*, and *Staphylococcus albus* may be present in small numbers. We have already seen that this tends to favor healing rather than to retard it.

The edges of the wound very soon show that they are under the influence of a stimulant. Two types of cell divide actively, the connective-tissue cell and the vascular endothelial cell. In both, mitotic figures may be seen, particularly in the former. (Fig. 50.) The connective-tissue cell or fibrocyte of adult fibrous tissue is little more than a narrow nucleus surrounded by a thin layer of cytoplasm and wedged between dense bundles of collagen fibers, but it rapidly changes into a plump fusiform cell with a large nucleus and well-developed cytoplasm which may end in branching processes. The sudden change from complete quiescence to extreme activity denotes the action of a powerful stimulant.

The mode of growth of the fibroblasts may best be studied by the method of tissue culture. The colonies of fibroblasts in culture medium tend to grow toward one another, as if the cells of one attracted the cells of the other. The coagulated plasma between the edges of the wound plays the part of a medium into which the fibroblasts grow and establish connection with those on the other side. Carrel has studied the motion of the fibroblasts in tissue culture by means of the cinematograph. The cells when photographed and projected on a screen can be seen to move through the medium in straight lines. The anterior process streams through the medium; then the nucleus and cytoplasmic body move forward. From such a picture it is easy to understand how the fibroblasts will rapidly unite the opposing surfaces. In culture the fibroblasts are seen always to keep in touch with their fellows, thus differing from the macrophages which wander about and live as independent units.



FIG. 50.—Proliferating fibroblasts, one of which shows a mitotic figure.  $\times 800$ .

The fibroblasts proceed to lay down collagen fibers. (Fig. 51.) It is difficult to be certain of how this is done, but it appears as if there was a continuous splitting off of the peripheral layers of cytoplasm, so that an ever-increasing thickness of collagen is formed between the cells. The fibril formation takes place at the expense of the cell bodies



FIG. 51.—Fibroblasts separated by scanty collagen.  $\times 275$ .

until finally these are represented by a thin, drawn-out nucleus surrounded by a delicate layer of cytoplasm. The collagen fibers form wavy bundles of *scar tissue*. (Fig. 52.) By this process of fibroblastic proliferation and immigration together with the formation of fibrils of increasing density the two surfaces of the wound are firmly sewn

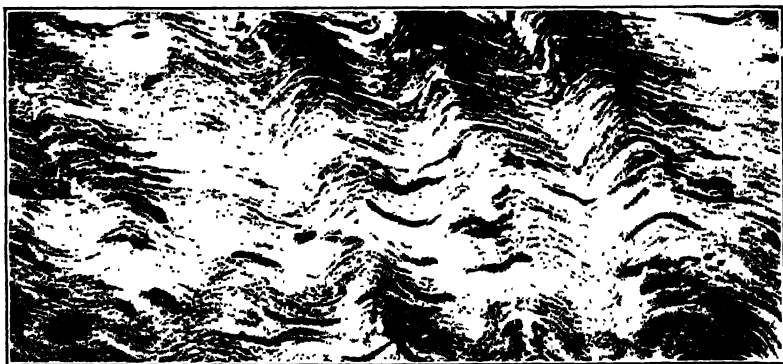


FIG. 52.—Scar tissue. Bundles of collagen fibers, between which are flattened fibroblasts.  $\times 400$ .

together. When the fibers are fully formed they shorten, and this contraction continues for some months, so that the scar which was at first raised becomes puckered.

Synchronously with the fibroblastic proliferation there occurs a proliferation of vascular endothelium. Protoplasmic buds are formed

from the preëxisting endothelium, and these establish connections with other buds until a branching network is formed. The buds become hollowed out, and a lumen is established which is continuous with the lumen of the parent capillaries. Marked vascularity is a fundamental characteristic of tissue undergoing repair, for an abundant blood supply is needed for the rapidly growing cells. The scar which first forms is therefore red. When repair is complete the stimulus to proliferate is withdrawn, a high degree of vascularity becomes unnecessary, and the vessels gradually disappear, so that the scar is avascular and white.

Pullinger and Florey using the transparent chamber in the mouse's ear introduced by Smith, found by direct observation that lymphatic capillaries proliferate in the same manner as the bloodvessels. A remarkably rich capillary network is established in ten to twelve days which can be demonstrated by injection. These new lymphatics no doubt play an important part in removal of the exudate. As healing proceeds they retrogress and finally disappear.

The epithelium from the sides grows over the narrow gap. It might be thought that the new epithelial cells were produced by mitosis. This is not the case. The defect is made good by the migration or sliding of cells from the edge of the wound. Mitoses are found regularly at some distance from the edge. At first the epithelial layer is thin and bluish in color, a mere layer or two of cells, but soon it becomes thick and white. The specialized structures of the skin such as hair follicles and sweat glands are not replaced. The scar is pale, without hair, and without sweat.

The time at which the various steps occur differs with differing conditions, but on an average it may be said that fibroblastic and endothelial proliferation occurs by the end of twelve hours, the epithelium has covered the surface and the edges are firmly sewn together by the fourth day, and at the end of three weeks there is fully formed non-vascular scar tissue. The active process of primary union takes about five days, and nothing but a thin line of connective tissue remains to indicate the site of the wound. If the wound is irritated there will be a more abundant exudate, more fibroblasts are formed, and the scar will be thicker. If the wound is badly infected suppuration will occur, and there will be no primary union.

**Healing of an Open Wound.**—When there is loss of substance the fibroblasts are unable to sew the surfaces together, and the gap is filled from below by a mass of young vessels and cells called granulation tissue. This is healing by granulation as opposed to healing by primary union. In time the granulation tissue becomes organized, *i. e.*, converted into fibrous tissue, a process known as cicatrization. Epithelium covers the surface, and the gap is closed.

The gap is first filled with a mixture of coagulated blood, fibrin, and inflammatory exudate, and upon this scaffold the fibroblasts and vascular endothelium build the granulation tissue. (Fig. 53.) The process commences at the base and works to the surface, so that the

youngest tissue is always at the surface. It is on the surface that the granulations are formed which give the name to the whole mass of young vascular connective tissue. When the surface of a clean open wound is examined at the end of the second day it is seen to be covered with tiny red granules, so that it has the appearance of the pile of rough velvet. This red, finely granular surface is an indication of normal and healthy healing. Such a surface is highly vascular and bleeds very readily. If a dry gauze dressing sticks to the surface and is then torn off, the capillary loops are ruptured, and the process of healing is materially interfered with.



FIG. 53.—Granulation tissue. Young vascular connective tissue consisting of new capillaries and fibroblasts, together with many inflammatory cells.  $\times 350$ .

In addition to the fixed cells of the part (fibroblasts and vascular endothelium), wandering cells also form an important element of granulation tissue. In the early stages these are mainly polymorphonuclear leucocytes, which migrate from the new capillaries in response to the irritation and appear on the surface in large numbers in the scanty exudate which our forefathers used to call "laudable pus." They doubtless serve to keep the surface free from infection. In the later stages and in the deeper layers the wandering cells are mainly macrophages and lymphocytes. The macrophages provide an even greater protection than the polymorphonuclears, for it can be shown experimentally that if an aseptic inflammation be produced and infection be added later, the substances which call forth macrophages in the aseptic inflammation give much better protection than those which call

forth polymorphonuclears. Not until the leucocytes have overcome the infection does the epithelium begin to cover the surface, and true healing can be said to have commenced.

On account of its cellularity a granulating surface has a remarkable power of resisting bacterial infection. It presents so powerful a barrier that septicemia (blood invasion) cannot occur once an intact wall of granulation tissue has been formed. Billroth demonstrated this experimentally as long ago as 1865 by applying septic dressings soaked

in putrid pus to the surface of a granulating wound. No infection resulted; but if the dressings were stitched in position, the stitch holes in the healthy skin at once became infected. Burrows found that when virulent streptococci were injected into the freshly epilated skin of a rabbit severe inflammation resulted, but that if there was an interval of five days between the two procedures, no inflammation developed. Although a granulating wound offers marked resistance to infection, this does not include the spirochete of syphilis, which can readily penetrate such a surface. Chesney and his associates excised a piece of skin from the back of a series of rabbits, and three weeks later they injected *Spirochaeta pallida* into the testicle. In nearly every case an indurated syphilitic lesion developed in the scar on the back in the course of a month. A colloid such as tetanus toxin is not absorbed from a granulating surface, if an interval of at least five days be allowed to elapse before the application of the toxin. The toxin is not destroyed, for if the wound is scarified and bleeds, the animal will invariably develop signs of tetanus. (White.) Crystalline substances in solution are rapidly absorbed, probably on account of the great vascularity of the surface, so that death may follow the application of a poisonous substance like corrosive sublimate, and it is said that opium will occasion sleep nearly as quickly as when given by mouth.

The granulation tissue grows in maturity from below upward. In the superficial layers the fibroblasts run at right angles to the surface and therefore parallel to the vessels, but in the deeper parts of the wound where the process is older they are arranged parallel with the surface, and eventually all the fibroblasts and the fibers which they produce run in this direction. The direction depends largely on the pull which is exerted on them. If this be altered experimentally, the direction of the fibroblasts will be correspondingly changed.

When the wound is aseptic the epithelium will grow in from the edge in two or three days, first as a delicate blue pellicle, gradually becoming thick and opaque. To say that the wound is aseptic does not mean of course that it is bacteriologically sterile. If there is sepsis and active inflammation the surface is bathed in pus, and the epithelium shows no sign of activity. In a chronic ulcer, where for some reason healing is long delayed, the epithelium sends long processes down into the deeper tissues. These may appear to be detached from the surface in a microscopic section, and may be very suggestive of carcinoma. In some cases a malignant growth may actually commence in such a chronic ulcer.

When the surface is covered by epithelium the process of devascularization begins. The new vessels being no longer needed gradually disappear, and the scar which is first red and angry-looking becomes white and bloodless.

**Healing of an Abscess.**—All repair is fundamentally the same, whether in an open wound or in an abscess in the center of the kidney. If the infection is destroyed, attempts at repair begin. These are much more successful if the pus can discharge on to a surface, as into the

pelvis of the kidney. If the cavity is small it becomes filled up first with granulation tissue, then with scar tissue. If the cavity is large it cannot be filled in, but a fibrous wall is built around it. Healing after appendicitis takes the same course, first granulation tissue, then scar tissue.

**Organization of an Exudate on a Serous Membrane.**—When a serous membrane such as the peritoneum is inflamed the endothelial covering is destroyed, and an exudate is formed on the surface consisting mainly of fibrin. This is invaded by fibroblasts and new capillaries, so that the exudate is replaced by granulation tissue, which in turn is fibrosed. The surface endothelium may again cover the fibrous patch, restoring the integrity of the membrane. Or two fibrinous surfaces, *e. g.*, two inflamed loops of bowel, may coalesce and become adherent. The fibrinous adhesions become fibrous, and although the sides of the adhesions are clothed with endothelium the integrity of the surface cannot be restored, and the adhesions are permanent. The fibrous bands contract, and may cause kinking and obstruction of the bowel.

**Organization of a Thrombus.**—A blood clot or thrombus in a vessel undergoes the same changes as an inflammatory exudate. It is invaded from the side of the vessel by fibroblasts and endothelial buds. New capillaries are formed, and a vascular connective tissue gradually takes the place of the clot. As cicatrization occurs the fibrous mass may shrink from the vessel wall, so that a space is formed which becomes lined by the endothelium of the vessel. In this way a certain flow of blood may be reëstablished through the vessel. Occasionally new channels are opened through the clot; these become lined with endothelium, and the clot is said to be canalized.

A brief summary of the healing process in different tissues is all that need be given there. Greater detail will be found in the chapters devoted to the individual organs.

*Epithelium* as it occurs in the skin is repaired rapidly and completely. The more specialized epithelial skin structures such as hair follicles are not replaced. *Connective tissue* is completely replaced, as fibroblasts are the cells of connective tissue. *Elastic tissue* is replaced very slowly, but fairly completely. *Fat* destroyed in a wound is usually not reformed, but if the fat cells are only partially destroyed new cells smaller in size and containing fine droplets may be formed within them. *Cartilage* is so avascular that healing is very slow and imperfect. If the damage is at all extensive, the replacement is by scar tissue. New cartilage can be formed from the cells of the perichondrium, and small gaps may be filled in this way. Healing in *muscle* depends on the kind of muscle. Plain muscle and heart muscle fibers do not regenerate; union of the divided parts is by scar tissue. Striated muscle has greater reparative power. The extent of regeneration depends on the type of injury. In an incised wound with no loss of substance the nuclei of the sarcolemma proliferate and form multinucleated syncytial masses (Fig. 54) while the sarcous substance puts out bands which bridge the gap and eventually become striated. On

the other hand when the muscle fibers have been destroyed the débris is removed by mononuclear phagocytes, which may form giant cells, and the gap is closed by fibrous tissue. (Fig. 55.) *Tendon* is very avascular so that healing is very slow, but it is remarkably complete, though it



FIG. 54.—Regeneration of muscle showing syncytial masses of sarcolemma.  $\times 300$ .

may take as long as two months. If the gap is small it is filled completely by tendon cells; if large scar tissue has to be used. Sepsis is fatal to healing, because necrosis occurs so readily in the non-vascular tendon. Injury of a *serous membrane* is repaired by fibrous tissue which becomes covered by the endothelium of the membrane. A fibrinous exudate is formed on the surface at the site of injury, and the two sur-

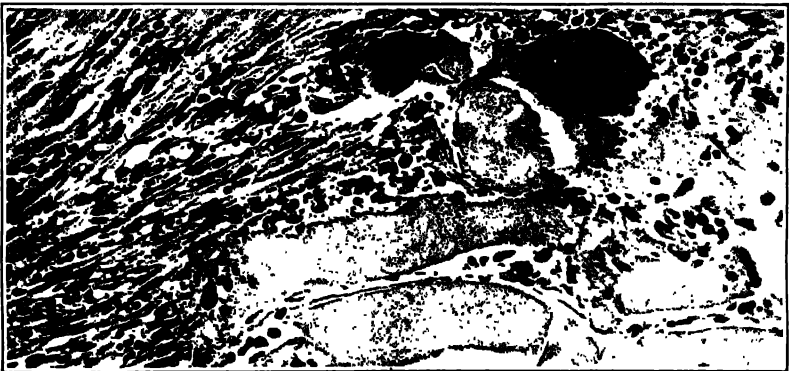


FIG. 55.—Necrotic muscle fibers being removed by giant cells and replaced by fibrous tissue.  $\times 180$ .

faces tend to be united by adhesions which are at first fibrinous but soon become converted into fibrous tissue. A *mucous membrane* is repaired quickly and well. The surface epithelium is completely replaced, and simple tubular glands can be reformed from this epithelium,

but complete restoration of such glands as those of the stomach only occurs when portions of the glands have escaped destruction. Wounds of the *liver* are repaired by scar tissue. The liver cells have great power of regeneration, and this is seen in the necroses of the liver such as acute yellow atrophy and cirrhosis where the lesion is primarily one of the epithelial cells rather than in wounds and abscesses. In the *kidney* there is no regeneration of glomeruli or tubules already destroyed so that repair is confined to the formation of scar tissue. The *central nervous system* has no power of true regeneration. When a neurone is killed it is not replaced. A wound of the brain is filled by neuroglia which proliferates readily, and to a small extent by the connective tissue which accompanies the bloodvessels. The *peripheral nerves*, on the other hand, have remarkable powers of regeneration, a process which will be considered in detail in the chapter on The Nervous System.

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## CHAPTER VI

### INFECTION AND RESISTANCE

INFECTION signifies invasion of the tissues by pathogenic micro-organisms or animal parasites, and the results both local and general which follow upon that invasion. These results vary enormously. They may remain strictly local, as in a skin abscess or boil due to staphylococci, or they may be general, as in blood invasion by streptococci. There may be an acute inflammation produced by the pyogenic cocci, or a slow proliferative change as in tuberculosis or syphilis, or the microorganisms may remain at the site of invasion but exert a toxic action on a distinct organ such as the brain (as in tetanus). The same infection may produce very different effects in different persons. These variations depend on two great factors, the virulence of the microorganisms and the resistance of the patient. The subject may conveniently be divided into two sections, infection and immunity.

The *path of infection* may be by one of three routes: (1) surface (skin and mucous membrane), (2) inhalation, (3) ingestion. The *surface* need not be broken, for anthrax bacilli may infect the skin, staphylococci may penetrate a hair follicle and produce a boil, the spirochete of syphilis can pass through a normal mucous membrane. Surface invasion may be due to the bites of insects; such a disease as malaria is acquired in this way. By inhalation the germs are taken into the respiratory tract, as in pneumonia and tuberculosis. Infection by ingestion is seen in such diseases as typhoid, dysentery and cholera.

The skin acts as a mechanical barrier to infection, but it does more than that, for it is able to free itself rapidly from the majority of bacteria which impinge on it. Arnold found that when a broth culture of *B. coli* or *B. typhosus* was painted on the skin all the bacteria had disappeared in the course of ten minutes. The same is true of other organisms, although the time may be considerably longer. Dirty skin, however, has little power of autosterilization. The property may be due to the chemical action of the sweat. This is only true of those bacteria which do not form part of the normal flora of the skin. No amount of washing or use of the ordinary disinfectants of surgical and obstetrical practice will free the skin of the staphylococci and diphtheroids which normally vegetate there.

This matter of a *normal bacterial flora* is one of great importance. As Topley remarks: "The surfaces and portals of entry are in no sense virgin soil on which any invading bacterium can easily gain a foothold. The various skin and mucous surfaces are differentiated from one another by the nature of the epithelium that covers them,

by the acidity and alkalinity of the fluids in which they are bathed, by the frequency, rate and direction of the currents in the supernatant fluid, probably by the presence and nature of lytic or bactericidal substances of which we as yet know little, and in many other ways." As a result each region of the body has developed a highly distinctive flora. Thus on the *skin* we find staphylococci and diphtheroid bacilli; in the *mouth* and *pharynx* a wide variety of bacteria, particularly *Streptococcus viridans* and Gram-negative cocci, frequently diphtheroid bacilli, pneumococci, and bacilli of the influenza type, occasionally hemolytic streptococci; in the *stomach* none because of the acid gastric juice; in the *duodenum* Gram-positive cocci; in the *jejunum* cocci, and *B. coli*; in the *large bowel* varied aerobic and anaerobic species; in the *vagina* a highly distinctive flora consisting almost entirely of acidophil bacilli of the Döderlein type.

**Localization of Infection.**—Once infection has occurred, its localization depends on a number of factors. When the organisms have entered the body, as through a wound in the skin, they may be held more or less *in situ* or they may drift through the tissues with amazing rapidity. It is evident that the consequences to the patient will be entirely different in the two cases. Local fixation is seen in a striking form in an animal which has been actively immunized, and of course even more so in an animal which is naturally immune. When tubercle bacilli are injected into the skin of a normal animal they spread from the site of inoculation in the course of an hour, so that excision of the area after that time fails to save the animal, and when placed in the peritoneal cavity they are found in the regional lymph nodes in the course of five minutes. If the animal has previously been immunized, the bacilli remain, for a time at least, at the site of inoculation.

Menkin has shown that fibrin formation may play an important part in localizing an infection in the early stages before phagocytes have time to arrive. If an aseptic peritonitis is first produced and iron salts are then injected into the peritoneal cavity, the iron does not appear in the lymphatics and lymph nodes, whereas in a control animal a marked Prussian blue reaction is given by the regional lymph nodes. The same is true of bacteria. Menkin is of the opinion that the local fixation is due to the formation of a fibrinous network both in the lymphatics and the tissues, although many lymphatics still remain open so that the lymph flow from the part may be accelerated, as Drinker has demonstrated. The network of fibrin is abundant in staphylococcal infection, scanty or absent in streptococcal infection, thus accounting for the localized character of the former and the spreading character of the latter.

The beautiful experiments of Rich are of particular interest in this connection. Working with the pneumococcus, an organism which rapidly spreads through the tissues of the rabbit and kills it in from twenty-four to thirty-six hours, he compared the local lesions produced by inoculation of normal animals and of animals which had been rendered immune but not allergic to the pneumococcus. In the nor-

mal animal the organisms at once began to drift through the tissues as each one divided into two and the pair separated, while in the immunized animal they rapidly clumped together and remained *in situ*, as if glued to the part. (Fig. 56.) The process is one of agglutination, an increase of stickiness, as a result of which the bacteria adhere to one another and to the tissues with which they come in contact. Large clumps were formed in the course of thirty minutes, but at that time there was no inflammatory exudate, no fibrin formation. It is evident that local fixation cannot be attributed to allergic inflammation nor to the formation of a mechanical barrier; it is a specific antibody effect.

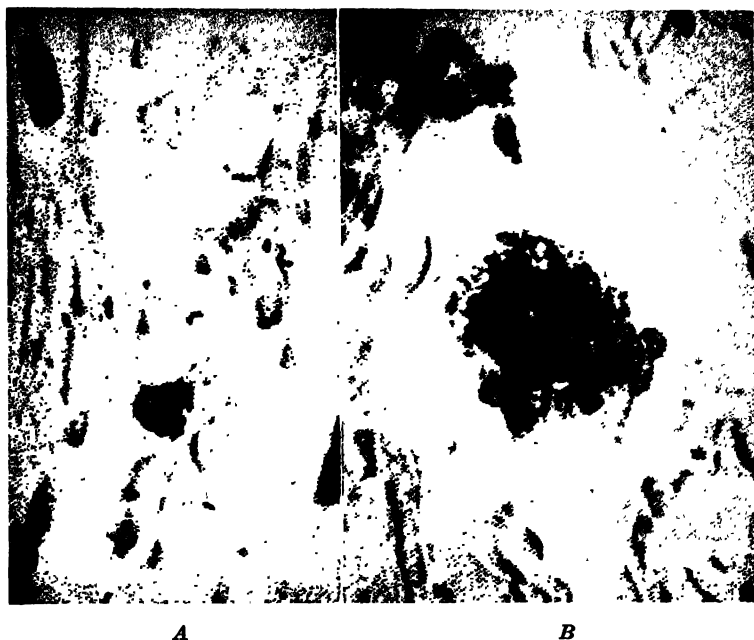


FIG. 56.—*A*, Site of infection in non-immune rabbit four hours after injection of pneumococci; cocci drifting through the tissue; *B*, the same in an immune rabbit four hours after injection; the proliferating cocci are clumped together. (Rich, Bull. Johns Hopkins Hospital.)

In the immune animal the bacteria become opsonized, as a result of which they adhere not only to each other, but also to the surface of the leucocytes. The same local fixation occurs if the bacteria and immune serum are mixed before being injected. The bacteria are held locally until the inflammatory exudate has had time to form, when phagocytosis is seen to be much more marked than in the non-immune animal, again owing to the action of opsonins. This is evidently the mechanism by which an infection is localized in man. In the human patient streptococci and pneumococci tend to produce spreading lesions, while staphylococcal lesions tend to be localized, and it is interesting

to note that normal human serum contains agglutinins to the staphylococcus, and that these organisms do not grow by nature in clumps in a fluid medium containing no serum. Finally, it must be pointed out that no matter how immune the animal (and some of Rich's rabbits resisted several million times the lethal dose), the bacteria continued to proliferate although clumped together; they were not killed by the antibodies. It was only when the phagocytes arrived that they were destroyed.

So far we have discussed the mechanism by which bacteria which gain entrance to the tissues are held locally and prevented from setting up a general blood infection. Now we may turn to the converse of this question. When organisms are circulating in the blood their localization in the tissues depends largely on the permeability of the capillaries, which in turn is governed by such a factor as trauma, causing the liberation of histamine and resulting local capillary paralysis with increased permeability. When trypan blue is injected intraperitoneally in rats, and the animals are then struck on the head repeatedly, the dye is found to be localized in the brain (Macklin). When the dye is injected intravenously and a hot-water bag is applied to the abdomen, the dye will stain not only the abdominal wall but also the subjacent coils of bowel. As the result of a similar mechanism, bacteria circulating in the blood will tend to become localized at the site of injury. Should hemorrhage have occurred, the bacteria will leave the blood stream still more readily. A common clinical example is the relation of trauma to acute osteomyelitis.

The question of localization of infection does not depend, however, entirely on the tissues and fluids of the body. The bacteria themselves have something to say on the matter of invasiveness. Duran-Reynals has shown that invasive strains of staphylococci and streptococci contain a soluble factor which can be extracted, and which markedly increases tissue permeability and enhances the infections produced by these organisms as well as by other bacteria. This is known as the *Duran-Reynals* or *spreading phenomenon*. Non-invasive strains of the same species of staphylococci and streptococci do not contain this factor. A similar spreading factor is contained in large amounts in the normal testicle. The factor has been shown by Chain and Duthie to be hyaluronidase, an enzyme which acts on hyaluronic acid, a substance to which some body fluids owe their viscosity.

**Focal Infection.**—Focal infection is a fact of great importance in medicine, but it must not be confused, as is so often done, with *elective localization*, which is only a theory with little experimental basis, nor again with a focus of infection. By focal infection we mean the setting up of secondary infections at a distance, owing to invasion of the blood stream from a primary focus. When tubercle bacilli are carried from a bronchial lymph node to the kidney and there produce a tuberculous lesion, the process is one of focal infection. The term has come to be associated in the medical mind almost solely with streptococcal infection, and in particular with Rosenow's theory of the elective

localization of streptococci. According to Rosenow, elective localization may occur within a single species of bacterium, *i. e.*, a race of bacteria may become adapted to proliferate in a particular tissue, this tendency being accentuated by repeated passage. His work has been confined to the production of streptococcal lesions in rabbits. Streptococci which in man are responsible for articular rheumatism produce lesions in the joints of the rabbit, a strain isolated from a gastric ulcer causes ulceration in the rabbit's stomach, and so on. The chief objection to this work is a statistical one. Streptococci isolated from a gastric ulcer do not produce lesions only in the stomach, the same being true for the joints, heart valves, etc. As Topley and Wilson remark, the differences recorded are differences in frequency distribution; they are quantitative, not qualitative. The reader should consult the excellent critical review by Holman covering the entire subject of focal infection and elective localization. He points out that the factors determining the localization of bacteria circulating in the blood depend on local conditions rather than on the bacteria themselves. There is, of course, a selective localization when one type of organism is contrasted with another. The meningococcus infects in particular the meninges, the gonococcus the genital tract, the typhoid bacillus the lymphoid tissue of the abdomen, etc. But tubercle bacilli isolated from the kidney do not produce only renal lesions when injected into an animal, and the same is true of the streptococci.

**Results of Infection.**—Bacterial invasion usually produces a local lesion at the site of entry, but there may be no indication of a lesion to the naked eye. Tubercle bacilli when placed in the eye may cause enlargement of the cervical lymph nodes with no disturbance in the eye. The same bacilli may pass through the wall of the bowel and infect the mesenteric lymph nodes. An unrecognizable lesion of the finger may give rise to fatal streptococcal blood poisoning. Even in these instances, however, microscopic examination will show some change in the tissue.

The common result of infection is *local inflammation*. This may be acute, as in the case of the pyogenic bacteria, or the reaction may be chronic in type, as in tuberculosis and syphilis. The microorganisms may be killed by the inflammatory leucocytes, so that the infection ceases there and then. Sometimes the infection becomes quiescent but does not die out, and may at any time reawaken into activity; a chronic abscess of bone or a quiescent tuberculous lesion in the lung is a sleeping volcano of this kind.

Instead of remaining localized and giving rise to an abscess, the infection may *spread*. Streptococcal infections show a marked tendency to extend, and the most virulent strains may spread at an appalling speed. The infection may travel along the interspaces of the tissues, giving rise to a spreading cellulitis. An even more rapid spread may occur along the lymphatics, and lymph nodes at a distance may be infected in a few hours. The microorganisms may be arrested and destroyed in the lymph nodes, they may cause suppuration and

breaking-down of the nodes, or they may pass through the nodes and enter the blood stream. The infection then becomes a general blood infection.

**Septicemia and Bacteremia.**—Septicemia is a commonly used term, but it is most difficult to define. When microorganisms circulate in the blood stream the patient has a bacteremia. This does not necessarily mean that he is ill. It is probable that bacteria continually gain access to the blood from the mouth and through the intestinal wall, but the life of these bacteria is short. When bacteria are injected into the subcutaneous tissue of an animal they can be found within a few minutes in the liver, heart, and lungs, but they soon disappear. It is probable that in all infections a bacteremia occurs at some stage. In typhoid fever the blood is flooded with bacilli at the beginning of the illness and the same is true of lobar pneumonia. To none of these conditions is the term septicemia applied. Septicemia is a clinical rather than a pathological conception. In addition to the presence of a bacteremia, the patient manifests symptoms which are known as septicemia, such as high fever, chills, and petechial hemorrhages in the skin. The prognosis at once becomes much more serious. Microorganisms are present in the blood in large numbers. They are readily demonstrated by blood culture, and when the infection is very heavy they can be seen in blood smears, as in some cases of streptococcal and meningococcal septicemia. Their great numbers may be due partly to multiplication in the blood, but mainly to a continual pouring of bacteria into the blood stream from some focus of infection. Good examples are the heavily infected vegetations on the heart valves in acute endocarditis, the thrombosed open blood sinuses of the septic puerperal uterus, and the bacteria-laden bone-marrow of acute osteomyelitis. When the focus is removed or even drained, as in osteomyelitis, the bacteria may rapidly disappear from the blood stream.

**Pyemia.**—Pyemia is one step further in the septicemic process. Clumps of bacteria lodge in the tissues and set up secondary abscesses in the kidney, liver, myocardium, skin, etc. (Fig. 57.) The condition is usually caused by thrombi infected with pyogenic bacteria breaking-up and being discharged into the circulation, only to be arrested when they reach the capillaries of the lungs, the glomeruli, etc.

The development of septicemia depends on the balance between infection and resistance. The more virulent the organisms and the weaker the resistance, the more likely is septicemia to occur. Resistance bears no relation to "general health" in the common meaning of the term, but to immunity produced by minimal infections. A pathologist or surgeon returning in robust health from a holiday is in greater danger from streptococcal infection than one who has finished a long winter's work involving constant exposure.

Any pyogenic microorganisms may cause a septicemia, but at least 50 per cent of the cases are due to hemolytic streptococci. The other common invaders are staphylococci, pneumococci, *Bacillus coli*, and *Bacillus pyocyaneus*. Perhaps the most rapidly fatal of all the septi-

cemias is that due to the meningococcus, fortunately comparatively rare.

The *postmortem appearances* in streptococcal septicemia are important. Rigor mortis is slight or absent, and postmortem decomposition is rapid. The blood is fluid and dark, and does not coagulate. Owing to hemolysis of the red blood cells the lining of the heart and large vessels is stained red, and jaundice may have been apparent during life. The heart is dilated, and the myocardium and muscles are friable and flabby. The spleen is enlarged, soft, and friable, a condition known as acute splenic enlargement. The walls of the capillaries are injured, so that there are petechial hemorrhages in such serous membranes as the pleura, pericardium, and endocardium. Many

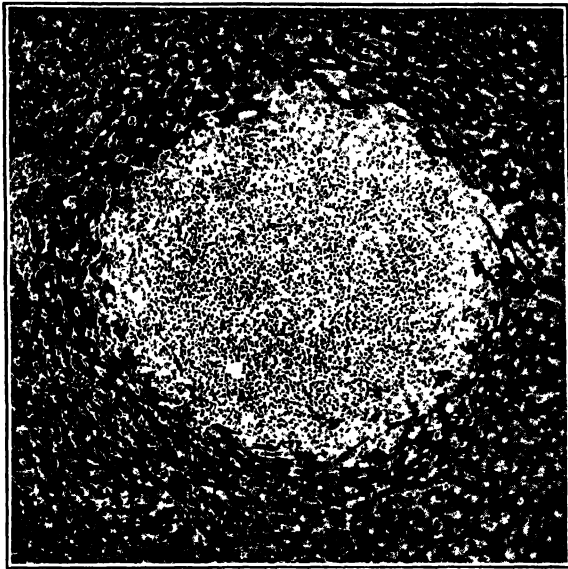


FIG. 57.—Pyemic abscess in liver.  $\times 200$ .

of these signs may be absent, so that in some cases the postmortem diagnosis of septicemia may present great difficulty to the pathologist. In pyemia in addition to the usual lesions of septicemia small yellow abscesses are present in the lungs, heart, kidney, and other organs, usually just under the surface.

**Toxemia.**—In septicemia and pyemia many organs show evidence of the action of toxins. These changes may be equally well marked even when no microorganisms have entered the blood stream. Diphtheria is an excellent example. Here the bacteria remain in the mucous membrane of the throat, but profound toxic changes are found in the heart, liver, and kidneys. These changes are degenerative in character, ranging from cloudy swelling and fatty degeneration to

necrosis and disintegration of the cells. In toxemias of long duration amyloid degeneration may develop.

**Our Present Conception of Resistance.**—Although our understanding of these matters is but that of children, despite the use of a multitude of high-sounding words (at least so it appears to the writer), we can yet express some general ideas as to why some persons resist infection or quickly recover from it, while others do not. Resistance to infection depends upon three great factors: (1) humoral antibodies, (2) phagocytosis, and (3) the immunological (*i. e.*, chemical) behavior of certain tissue cells. The humoral and cellular forces work hand in hand, and the background of all the antibodies is formed by the cells of the reticulo-endothelial system.

Of the *antibodies* the most important appear to be antitoxins, bacteriolysins, and opsonins. Antitoxins do not rid the body of infection, but they cause the symptoms to clear up. Bacteriolysins (immune bodies) do not act directly on the bacteria, but merely play the part of an amboceptor whose hands join together the complement and the germ, to the destruction of the latter. The patient must therefore have enough of the all-important complement as well as an abundance of immune bodies if he is to recover. Opsonins must be present to sensitize the bacteria, so that these may be devoured by the phagocytes. The important part which the antibodies (opsonins and agglutinins) play in the localization of infection has already been considered. They serve to detain the invading bacteria until the leucocytes can collect in sufficient numbers at the site of infection to make their presence felt.

A discussion of the antibodies which form the basis of immunity would be out of place in a book of this type. The subject is considered in detail in works on bacteriology and immunology. From the general standpoint, however, it may be said that it is now known that antibodies consist of globulins, and that their formation depends on the general protein reserve. For this reason the question of diet has come to assume importance in resistance to infection. Under conditions of famine the protein reserve falls to dangerously low levels, and there is a corresponding drop in resistance to bacterial infections. It is well known that under such circumstances there is danger of widespread epidemics.

The *phagocytes* are not merely the polymorphonuclear leucocytes, although these form the first line of defense. Of equal importance are the macrophages of the tissues, derived in turn from the reticulo-endothelial system. The fixed cells of this system play an important rôle in removing bacteria circulating in the blood. Vast numbers of organisms may be injected into the blood stream, but they rapidly disappear, and are found in the reticulo-endothelial filters of the liver, spleen, bone-marrow, and lungs. Here also the humoral factor must not be overlooked. If a large dose of pneumococci is injected into the blood stream of a rabbit (a highly susceptible animal), a blood culture fifteen minutes later will show enormous numbers of organisms, but if



antipneumococcus serum is injected into another vein at the same time the blood will be found to be sterile at the end of fifteen minutes. The sensitized bacteria are taken up partly by the circulating phagocytes, partly by the fixed reticulo-endothelial cells. This can be shown in the case of the liver by perfusing the liver with pneumococci suspended in saline solution or normal serum. None are retained. When a minute quantity of immune serum is added, there is complete retention of bacteria by the liver. These experimental observations on the removal of bacteria from the blood have been confirmed in man. Immediately after curettage for a septic abortion the blood may be loaded with bacteria, but there may be none 15 minutes later.

The factor of *tissue immunity* is perhaps the most important, although the hardest to understand. It provides the reason why some animals simply cannot be infected by microorganisms which are highly pathogenic to animals of another species. If a toxin or a virus has no chemical affinity for a cell, it cannot injure it, no matter in what quantity it may be present.

### ALLERGY

The body tends to protect itself against bacterial infection by certain processes which may be grouped under the common heading of immunity. But during the development of immunity there may appear a very different and indeed opposite type of reaction, namely, hypersensitiveness. This reaction is a hypersensitiveness to the *bacterial protein*, and an equally marked hypersensitiveness may be developed against any foreign protein (horse serum, egg albumen) which may be injected. The first injection produces no evident effect, but a second injection is followed by the development of striking and often dramatic phenomena which may be local or general in their manifestations. The interval between the two injections must be of a certain duration, at least a week or ten days, and it may be noted that this corresponds to the incubation period of many infectious diseases, *i. e.*, the time interval between the initial infection and the development of the tissue changes which produce the clinical phenomena of the disease. The condition of hypersensitivity is known as allergy, which means altered reactivity. Unfortunately the term has become one of the most abused in medicine. The factor best calculated to produce it is a chronic low-grade infection.

**Anaphylaxis** is a form of hypersensitiveness which differs from and yet is related to allergy. In allergy the reaction is a necrotizing, inflammatory one, whereas in anaphylaxis it is a musculo-spasmodic one. Anaphylaxis has been studied for the most part in the experimental animal, but it also has its human counterpart. Its principal manifestation is a spasmodic contraction of smooth muscle, chiefly of bronchioles and certain bloodvessels, as a result of which the animal passes into a condition of anaphylactic shock which may result in death. It is above all a hypersensitiveness of smooth muscle. Human anaphylaxis is much less striking, because man is, fortunately, far less sensitive than the guinea-pig. A person may, however, become

sensitized against horse serum (diphtheria and other antitoxins), so that a second injection may be followed by symptoms of anaphylactic shock and death.

Most of the experimental work has been done with non-bacterial proteins. As long ago as 1903 Arthus showed that when horse serum was injected into the skin of a rabbit which had been previously sensitized by injections of the same serum, a violent local reaction was produced, characterized by marked inflammation and necrosis and sloughing of tissue. This allergic inflammation with necrosis is known as the *Arthus phenomenon*. The essence of the reaction and, indeed, of allergy in general lies in the fact that the tissues are locally damaged and killed by an amount of protein which is harmless to the normal body. The injections need not be given at the same place; the first may be given intraperitoneally and the final one into the skin. It is evident that all the tissues become sensitized, and the allergic reaction is an antigen-antibody reaction in the cell itself.

Bacterial allergy is very similar in its reaction to the Arthus phenomenon, although the hypersensitive state cannot be transferred passively to a normal animal. It appears probable that in many, if not in all bacterial infections, hypersensitiveness develops *pari passu* with the development of immunity. Many destructive lesions which in the past have been attributed to the action of bacterial poisons are in reality due to hypersensitiveness to the bacterial proteins, although it must be admitted that allergy is a term often used to give a touch of mystification to ignorance. That the reaction is essentially a cellular one independent of circulating antibody is shown by the observations of Rich and Lewis on cells isolated from an animal rendered allergic to tuberculin and grown in tissue culture. When a minute amount of tuberculin is added to this allergic culture, the same tissue destruction and necrosis occurs which is seen in the living animal.

The *Shwartzman phenomenon* is a local tissue reactivity to bacterial filtrates. Shwartzman has shown that if a bacterial filtrate is injected into the skin, and the same filtrate is injected intravenously twenty-four hours later, a severe hemorrhagic and necrotizing inflammation develops at the site of the local injection. The preparing injection produces only a slight reaction. It may be made into the parenchyma of an organ such as the stomach or a joint. It can even be made into the vascular system of an organ, *e. g.*, injection into the renal artery after the renal vein has been clamped for five minutes. Lesions in the kidney can be produced when the preparing injection is made into the general circulation, probably because of the greater permeability of the glomerular capillaries. Renal lesions have developed as the result of a single intravenous injection in pregnant animals; this may possibly explain the diffuse symmetrical necrosis of the kidneys in eclampsia if pregnancy is regarded as a state of generalized increased reactivity.

The first change is marked venous and capillary dilatation and

engorgement, soon followed by severe hemorrhage, edema, and intense infiltration with leucocytes. The veins and capillaries are filled with thrombi, amorphous granular masses probably consisting of platelets. A large central area of necrosis develops in the affected skin or organ. It is possible that some hitherto mysterious inflammatory lesions may find their explanation in the Shwartzman phenomenon.

**Allergic Inflammation.**—There can be no doubt of the existence of allergic inflammation, a type of tissue response to the local interaction of antigen and antibody. This can be demonstrated in the experimental animal. It is more than probable that a number of human inflammations of uncertain nature and etiology are examples of a similar reaction. The general characteristics of allergic inflammation are acute onset, necrotizing arteritis, focal necrosis, and an inflammatory exudate mainly mononuclear in type, often with numerous eosinophils. Of particular significance is the absence of bacteria. Examples of conditions which may be allergic in nature are bronchial asthma, rheumatic fever, glomerulonephritis, periarteritis nodosa, Buerger's disease, and disseminated lupus erythematosus. When we come to study these conditions we shall find most or all of the above-mentioned features. It will be noticed that in most of them (including glomerulonephritis) the main tissue involved is part of the vascular system. In periarteritis nodosa the vascular lesions are remarkably similar to those seen in serum sickness in the experimental animal and in the rare cases observed in man (Rich). Fibrinoid necrosis of the arterioles is always suggestive of an allergic basis, and the walls of the vessels are often infiltrated with inflammatory cells.

**Sulphonamide allergy** deserves special mention. In 1917 Landsteiner showed that simple chemical compounds could become conjugated with serum proteins; they could thus become antigenic in character and capable of exciting an allergic reaction. This is true of the sulphonamide compounds, and it is now common knowledge that these substances may in certain hypersensitive persons produce toxic symptoms which are evidently allergic in character. The hypersensitivity is usually acquired as a result of previous exposure to the drugs, but it may be inborn. The worst offender is sulphathiazole. The clinical manifestations are fever, chill, a skin eruption, and failing renal function with anuria about a week after the administration of sulphonamides. The principal lesions are in the kidney, liver and heart, but almost any organ in the body may be involved, and the lesions are often widespread. They fall into the following groups: (1) focal necrosis associated with cellular infiltration, often amounting to a granulomatous reaction, the chief cells being histiocytes, lymphocytes, plasma cells, and eosinophils; (2) necrotizing arteritis similar to that seen in periarteritis nodosa; (3) severe parenchymatous degeneration in the liver and kidneys. More, McMillan and Duff, in a careful study of 22 cases, emphasize that all the lesions combine necrosis with activity of the

reticulo-endothelial system; they describe and illustrate a peculiar necrosis of the splenic trabeculae. An acute interstitial myocarditis may cause death in some cases.

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## CHAPTER VII

### BACTERIAL INFECTIONS

IN this chapter will be considered the diseases produced by pathogenic microorganisms. Many of these will be described fully in the section on Special Pathology in connection with the organs principally affected (pneumonia, dysentery, etc.). In such cases the condition will only be mentioned here in passing. In others the lesions affect many organs (tuberculosis), or the infection may be general rather than localized (the infectious fevers). These conditions will be considered here more fully. No attempt is made to give bacteriological detail, as that would merely usurp the function of a text on bacteriology, but a few of the principal features of the microorganisms will be mentioned in order to recall them to the reader's mind.

#### STAPHYLOCOCCAL INFECTIONS

The *Staphylococcus pyogenes* is a Gram-positive micrococcus which grows in small clusters like a bunch of grapes (*staphyle*, a bunch of grapes; *kokkos*, a berry). Two principal forms occur, *Staphylococcus aureus* and *Staphylococcus albus*. The former produces a yellow and the latter a white color on solid media. *Staphylococcus aureus* is the much more pathogenic of the two, *Staphylococcus albus* usually occurring as a harmless skin saprophyte. But it is a mistake to make the distinction too hard and fast, for the color-producing power of a given strain may vary widely. Moreover, although *Staphylococcus albus* usually does little more than cause stitch abscesses in the skin, it may produce a fatal septicemia.

The staphylococcus is a pyogenic organism, and its action as a pus producer has already been described in connection with inflammation and suppuration. It occurs normally on the skin, and is prone to produce skin infections, entering through cracks, abrasions, or even by way of the hair follicles. In staphylococcal lesions of deeper organs (kidney, bone) an active skin infection (boil) or one which has recently healed can usually be found. In human blood there are natural agglutinins to the staphylococcus, so that when the tissues are invaded the organisms tend to adhere together and to the surrounding structures. For this reason staphylococcal lesions are more likely to be localized than diffuse. The cocci produce a coagulase, causing marked formation of fibrin. This further limits the spread by blocking paths of dissemination, as shown by the fact that when a dye is injected it does not spread along the lymphatics. In all of these respects staphylococci differ from streptococci, which tend to invade mucous membranes, and produce a fibrinolysis that breaks down the defense barrier. Some strains of staphylococci, however, produce a soluble "spreading

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factor" which markedly increases the permeability of the tissues (Duran-Reynals' phenomenon). Under appropriate environmental conditions, of which the hydrogen-ion concentration is one of the most important, certain strains have the power of forming an extremely powerful exotoxin in culture. Broth filtrates are found to produce three effects which may be called the hemolytic, the necrotizing, and the killing. Injection of a small amount of toxin into the skin of the animal results in marked necrosis. The killing power of the toxin is its most striking characteristic; an extremely small quantity injected intravenously leads to death in a few minutes. The tragedy at Bundaberg in Queensland, when 12 out of 21 children, injected with diphtheria toxin-antitoxin mixture, died in the course of a few hours was due to contamination of the mixture with a toxigenic strain of staphylococci. The toxin can be detoxicated by the addition of formalin; the resulting product is called toxoid, and this still retains its antigenic property. Superficial staphylococcal infections apparently do not provide an adequate antigenic stimulus, for persons with repeated boils may show no increase of antitoxin in the blood.

**Botryomycosis.**—This is a peculiar form of staphylococcal infection, common enough in horses, cattle and pigs, but very rarely observed in man. The lesions, which show chronic suppuration and extensive fibrosis, involve chiefly the liver, and more rarely the genitalia and bones. In the liver there are large inflammatory masses containing many small cavities filled with pus. The characteristic feature is the presence of large colonies of staphylococci embedded in the pus cells and held together by a network of fibrin. Club-shaped masses project from the colonies in a manner reminiscent of the clubs in actinomycosis, so that the disease is also known as staphylococcal actinophytosis. Granulomatous lesions with epithelial and giant cells may be seen in the connective tissue (Berger).

### STREPTOCOCCAL INFECTIONS

Streptococci are Gram-positive microorganisms which grow in curved chains (*streptos*, curved). They form one of the most disease-producing groups. But it is a group, and a very complex one at that. It may be divided by the action on hemoglobin into two main subgroups, *hemolytic* and *non-hemolytic*. The latter usually produces a green color (methemoglobin) on blood agar (*Streptococcus viridans*), but many fail to do so. Lancefield and Hare point out that by means of precipitation with appropriate antisera the hemolytic streptococci can be divided into four groups, of which only Group A is responsible for human infection. About 7 per cent of normal persons living in England harbor Group A strains in the throat. Fully two-thirds of the hemolytic streptococci in the nose and throat do not belong to Group A and are therefore harmless for man. What Okell has termed the offensive weapons of the hemolytic streptococci are three in number: (1) An *erythrogenic* or rash-producing toxin, (2) *pyogenicity*, and (3) *invasiveness*. They vary in intensity from case to case. Many hemolytic streptococci produce a *fibrinolytic* principle, which is partly responsible for the invasiveness. Cultures added to human plasma clot cause liquefaction of the clot.

The streptococcus is usually a pyogenic organism and produces lesions which in general resemble those of the staphylococcus, but they tend to be more diffuse and spreading and are characterized by cellulitis, lymphangitis and lymphadenitis. The streptococcus unlike the

staphylococcus may invade a surface without producing a local lesion. A mere pin prick may introduce streptococci which cause a fatal septicemia. Other portals of entry are throat infections, tonsillitis, middle-ear inflammation, an infected tooth socket, puerperal uterine sepsis, etc. Some of the most dangerous infections are those of the hands of the surgeon or pathologist (owing to the heightened virulence caused by passage through the body of the patient) and puerperal infection (exhaustion of the patient, anemia, raw areas, etc.).

*Non-suppurative lesions* are often found as an aftermath of Streptococcus hemolyticus infections. These consist for the most part of focal collections of lymphocytes and plasma cells, but polymorphonuclear leucocytes and eosinophils may also be present. The lesions are best seen in from one to two weeks after the initial infection, particularly in young persons. G. K. Mallory and Keefer found such lesions in the heart, kidneys, liver, spleen, lungs and pancreas. They suggest that they are the result of an antigen-antibody reaction in the interstitial tissues, and may possibly be related to the Aschoff bodies of rheumatic fever.

The importance of *anaerobic streptococci* as disease-producers is now becoming recognized. They may cause serious inflammation in puerperal sepsis, acute appendicitis, chronic pulmonary infections, and even acute meningitis. The organisms are found in smears of the infected material, but naturally do not grow under ordinary cultural conditions. Another point that is apt to be misleading is that they are practically non-virulent for laboratory animals.

*Streptococcal fevers* are in general more serious than those caused by staphylococci. Endocarditis, puerperal fever, scarlet fever, and erysipelas are particular examples, the last-named being considered below. Streptococci often complicate other infections and may be the cause of a fatal termination (influenza, etc.). Streptococcal septicemia is marked by rigors, high fever, a large spleen (though this is often too soft to be felt), diarrhea, and the presence of albumin and red blood cells in the urine. There is no infectious disease in which anemia may develop so rapidly; the hemoglobin may fall to 30 or even 20 per cent.

The metastases differ from those of staphylococcal fever, the serous membranes being mostly involved in accordance with the diffuse nature of the infection. There may be suppuration of the joints, pleura, pericardium, meninges, and peritoneum. There is not much tendency to local abscess formation unless infected emboli (endocarditis, puerperal sepsis) are circulating in the blood.

It has long been known that non-suppurative lesions may follow at varying intervals of time such hemolytic streptococcal infections as scarlet fever, erysipelas and puerperal infection. They have been called *Nachkrankheiten* by German investigators. They are most marked in cases with persistent bacteremia. These late tissue reactions are more prominent and more frequent ten days or more after the onset of the infection. For these reasons it has been suggested that they

represent an antigen-antibody reaction (Mallory and Keefer). The lesions are most marked in the heart and kidneys, but they may occur in most of the viscera. The focal cellular reaction is predominantly mononuclear rather than polymorphonuclear.

**Erysipelas.**—This is an acute inflammation of the lymphatics of the skin caused by hemolytic streptococci with marked erythrogenic (rash-producing) power which enter through some break in the surface, often very minute. The face or scalp is the usual site, and it is probable that the starting-point is often a latent infection of the nose or nasal sinuses. The common idea that erysipelas is an extremely infectious condition is wrong. Unless there is a discharge from the skin there is no danger of infection. From the site of inoculation the infection spreads outward, producing a bright red indurated area with a characteristically sharp margin. Just beyond this margin the lymph spaces are crowded with streptococci. There is a curious absence of suppuration, the inflammatory cells which crowd the tissue being almost all lymphocytes or mononuclears. In the more severe cases the deeper tissues may be involved, with thrombosis, cellulitis, and suppuration. General constitutional symptoms such as high fever and leucocytosis are not due to a blood invasion by the streptococci but to the absorption of toxins produced locally. An erythrogenic antitoxin of value has been prepared against the streptococcus of erysipelas.

**Scarlet Fever.**—Scarlet fever or scarlatina is an acute infectious fever caused by a specific strain of streptococcus, characterized by a high temperature, sore throat, and widespread rash, followed by nephritis, otitis media, and suppuration of the cervical lymph nodes.

**Bacteriology.**—It has long been suspected that hemolytic streptococci had some causal relationship to scarlet fever, for these organisms were commonly found in the throat lesions, but there were difficulties in the way. Scarlet fever was apparently a toxic disease like diphtheria, but the streptococcus was not known to produce an exogenous toxin. The life-long immunity which commonly follows an attack did not correspond with what was known of other streptococcal infections. Finally there was the difficulty that the disease could not be reproduced in the lower animals.

The problem was solved by the contributions of many workers, but the coping stone was laid by George and Gladys Dick in 1923. These workers showed that hemolytic streptococci from scarlatinal throats produced a toxin which when injected into the skin of persons who had never had scarlet fever caused an erythematous reaction (Dick test). The disease is now regarded as a local infection of the throat by a specific strain of hemolytic streptococcus, with distant toxic manifestations (rash, nephritis, etc.). Unlike diphtheria, the germ of scarlet fever can invade the blood and set up suppurative lesions in various organs.

**Symptoms.**—The *throat* is always inflamed, but the larynx does not share in the inflammation. There may be an angina, an extremely severe inflam-



mation with tissue destruction and the formation of a membrane. In these cases middle-ear suppuration is very likely to occur owing to spread of the infection along the Eustachian tube. Swelling of the *lymph nodes* is constant, and indeed swelling of the lymphoid tissue throughout the body, so that the name of lymphatic fever has been suggested. There may be suppuration and abscess formation in the lymph nodes of the neck. The *rash* is of a generalized punctiform type. The mucous membrane of the tongue shows a similar condition so that it has a strawberry appearance (strawberry tongue). *Albuminuria* is common, but this must be distinguished from true nephritis which when it occurs comes on during convalescence. The *nephritis* is marked by edema of the face which becomes pale and puffy, by a rapidly developing general anasarca, and by oliguria, albuminuria, and blood and casts in the urine. The blood in scarlet fever shows a well-marked leucocytosis.

**Lesions.**—The lesions are in the main toxic in nature, but some of the complications may be suppurative owing to streptococcal invasion. The principal lesions are found in the skin, tongue, throat, and lymphoid structures. In the *skin* the vessels of the dermis are enormously dilated. This is due to vascular paralysis from the action of the toxin, and is not a true inflammatory reaction. There is no change in the epidermis at first, but later (fifth to tenth day) the epithelial cells are separated by an infiltration of polymorphonuclear leucocytes. When the rash has faded there is much desquamation, and the epithelium accordingly shows many cells undergoing mitosis. The *tongue* shows the same changes as the skin.

The *lymphoid tissue* of the lymph nodes, both superficial and deep, the spleen, tonsils, liver, etc., shows hyperplasia. The germinal centers are swollen, and the sinuses dilated and filled with endothelial cells. The *heart* shows cloudy swelling and fatty degeneration. *Toxic lesions* also occur in the liver, kidney, adrenal, and spleen. These take the form of injury to the vessel walls with secondary infiltration by mononuclear cells into the surrounding tissue.

*Nephritis* is a common complication of convalescence, coming on in the third week. It is an acute glomerulonephritis with the usual glomerular and tubular changes found in that condition. No streptococci are found in kidney, so that the nephritis is apparently toxic in origin. Rather rarely there is quite a different type of lesion, an acute interstitial infiltration with polymorphonuclear leucocytes. These lesions are described more fully in connection with Bright's disease. The prognosis of scarlatinal nephritis is remarkably good if the patient is kept in bed. It usually clears up in from three to six weeks, and uremia is quite uncommon.

**Chronic Streptococcal Infection.**—The acute and pyogenic manifestations of streptococcal infection are readily recognized. But there is a very important group of chronic infections which are believed to be streptococcal in nature, but in which bacteriological proof is much more difficult. The so-called focal infections belong to this class. Here there is a quiet focus of infection, usually in the mouth (teeth, tonsils,) naso-pharynx or accessory nasal sinuses, from which distant tissues may be affected either by toxins or by minimal doses of the organisms, as a result of which they become the seat of chronic inflam-

mation. The subject is a vast one, including as it does diseases of such debatable etiology as nephritis, chronic arthritis, chronic cholecystitis, etc. It cannot be discussed in detail here, but occasional reference will be made to it in the chapters which follow.

### RHEUMATIC FEVER

Rheumatic fever is a widespread infection of fibrous tissues affecting the joints, the heart, and other organs. It resembles syphilis in being a chronic, perivascular, long-continued infection with ups and downs. The first attack usually occurs in childhood. While in the adult it is the joint lesions which dominate the picture, in children these may be negligible and, indeed, overlooked, so that in later years it may not be possible to get a past history of rheumatic fever, but the heart always suffers. It is of children in particular that the saying holds true that "rheumatism is a disease which licks the joints, but bites the heart."

**Etiology.**—The cause of rheumatic fever is still uncertain. In 1900 Poynton and Paine recovered a small diplococcus from the blood and tissues in several cases, but only recently has opinion been strongly in favor of the *Diplococcus rheumaticus*. Some observers think that it is a specific strain of streptococcus, while others believe that a number of different strains of non-hemolytic streptococci may be responsible. The difficulty is to demonstrate the organisms in the lesions. Even when present they are not numerous, and the fluid from the joints is nearly always sterile. In support of the streptococcal origin of the disease is the fact that Clawson and others have succeeded in producing what appear to be rheumatic lesions in animals by the injection of non-hemolytic streptococci obtained from human cases. Rheumatic nodules of the skin were produced by direct inoculation into the skin.

Green examined the valvular lesions bacteriologically in 9 cases of acute rheumatic endocarditis. In 8 of these he succeeded in culturing *Str. hemolyticus* from the valves, and *Str. viridan.* in one. No bacteria were found in the heart's blood, nor were they obtained from the valves unless gross lesions were present. In 5 of the 9 cases the same strain of *Str. hemolyticus* was cultured from the throat during life as was present in the valvular lesions.

Coburn points out that the incidence of rheumatic fever parallels in a striking manner the incidence of hemolytic streptococci in the throat and also the incidence of streptococcal diseases such as scarlet fever in which the primary infection is in the upper part of the respiratory tract. This incidence is affected to a marked degree by climate. Both are common in cold, damp climates, but are almost unknown in many parts of the tropics. Both are common in the children of the poor, but rare in the children of the wealthy. A child who suffers from recurring attacks of rheumatic fever and streptococcal sore throat in the slums of New York remains well when transported to South America. In the western part of the United States rheumatic heart

disease is about ten times commoner in school children living in regions near the Canadian border than in those from regions near the Mexican border. From these observations Coburn concludes that the infectious agent which initiates the rheumatic process in *Streptococcus hemolyticus*, but that some other factor as yet elusive is required to complete the picture. This factor may be a vitamin or other food deficiency.

The absence or great scarcity of the organisms in even the most acute lesions is difficult to explain. It has been suggested particularly by Zinsser and Swift that allergy (bacterial hypersensitiveness) may play an important part in the production of the lesions. Swift has shown that when a chronic focus of streptococcal infection is established in the body, the tissues of an animal react violently to the most minute doses of the antigen, which may be either the streptococci themselves or their autolytic products. The principal feature of this reaction is edema, and this is the exudative lesion of rheumatic fever. The other rheumatic lesion, a proliferative one, must be due to the actual presence of small numbers of streptococci. In man the focus of infection is probably in the mouth and naso-pharynx (teeth, tonsils, nasal sinuses). The belief in the allergic basis of rheumatic fever is strengthened by the observation of Rich and Gregory that rabbits subjected to experimental serum sickness develop, in some instances, lesions which resemble in their basic characteristics those of rheumatic carditis.

We may sum up the matter by saying that there is a considerable mass of evidence in favor of a streptococcus (not necessarily a single specific strain) being the causal agent in rheumatic fever, the comparative absence of organisms in the lesions being explained on an allergic basis. The original lesions in the heart, etc., must be due to the presence of bacteria in the tissues, but a condition of hypersensitiveness is maintained by a focal infection in the mouth. In addition to the streptococcus, some additional factor is probably needed, and it is possible that in many cases this accessory factor may be a food deficiency.

**The Lesions.**—The fibrous tissues and certain serous membranes are attacked in rheumatic fever. A characteristic lesion is produced known as the Aschoff body. This corresponds to the miliary tubercle of tuberculosis. It is a proliferative lesion. Even earlier than the proliferation there is a degenerative change in the collagen (*fibrinoid degeneration* of Klinge), as a result of which the connective tissue assumes a lattice-like appearance like canalized fibrin. In addition there is an exudative lesion, and outpouring of serum. The second type of lesion is most marked in the joints, the first type in the myocardium. The remarkable effect of salicylates on the symptoms of rheumatism is well known. This effect is due to a lessening of the exudation. There is no action on the essential proliferative lesion.

The *Aschoff body* is seen in most typical form in the interstitial tissue of the myocardium. (Fig. 58.) It is the result mainly of proliferation, but the exudative element is also present. It may be just visible to the naked eye, but is often invisible. In the heart it is oval or lemon-

shaped. It is paravascular in distribution, being situated in relation to the adventitia of the small arteries, but it is at one side of the vessel and does not surround it.

There are four components of the Aschoff nodule. (1) A center of necrotic material (probably collagen), often quite small in amount. (2) Aschoff cells. These form the characteristic feature. They are large cells of the epithelioid type, usually multinucleated. They are probably derived from the histiocytes, members of the reticulo-endothelial system. Many are really giant cells, but they have seldom more than six or seven vesicular nuclei, and resemble the giant cells of Hodgkin's disease rather than those of tuberculosis. (3) Lymphocytes and plasma cells, with an occasional polymorphonuclear leucocyte. Polymorphonuclears may sometimes be so numerous that the

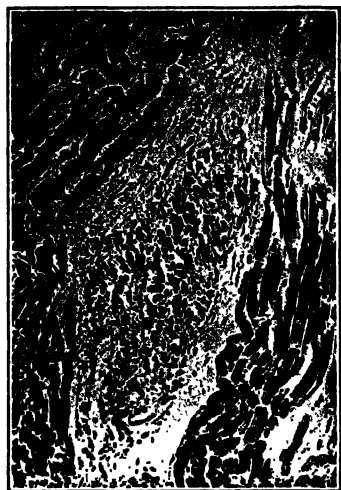


FIG. 58.—Aschoff body in myocardium. The oval body separates the heart muscle fibers.

lesion resembles an abscess; this is the exudative factor coming in. (4) Proliferation of fibroblasts with subsequent fibrosis. Edema, thrombosis, and swelling of the endothelium of the small vessels may also be present. Gross and Ehrlich have described what they call the life cycle of the Aschoff body, showing that a progressive series of changes can be recognized. Swelling of the collagen is a conspicuous feature of the earliest lesion. So also is the formation of a network of argen-tophilic reticulum fibers, as first pointed out by Klinge. They stress the very characteristic basophilic character of the cytoplasm of the Aschoff and allied cells. For the details of the life cycle the original paper should be consulted.

The special rheumatic lesions of the heart will be considered in connection with Diseases of the Heart. There is a pancarditis (myocarditis, endocarditis, pericarditis), and these "bites" in the heart are by far the most important part of the disease. Rheumatic fever is the chief cause of chronic valvular disease.

The *pharynx* may be regarded as the site of the primary lesion from which the rest of the body is infected. A sore throat frequently precedes or is associated with the onset of an attack of rheumatic fever. Fraser has found rheumatic nodules in the pharyngeal tissues during an acute attack. Similar nodules were present in the neighborhood of the tonsils, in the lingual and laryngeal tonsils, and in the upper deep cervical lymph nodes.

In the *skin* the rheumatic lesion is known as the subcutaneous nodule. It occurs in the deep fascia, especially over bony prominences, and is

composed of a group of Aschoff bodies. The general structure is the same though the outline is more indefinite.

In the *joints* the lesion is exudative, and it is to the sudden exudation in a tissue supplied so abundantly with small sensory nerves that the pain is due. Proliferative and vascular changes are also found in the synovial membrane, the capsule and the periarticular fibrous tissue. It is possible that the infective form of chronic arthritis may prove to be related to rheumatic fever. At least it appears to be a joint manifestation of a low-grade streptococcal infection.

The *brain* is affected and the patient suffers from chorea (St. Vitus' dance). The lesions are in no way distinctive. There are perivascular collections of round cells, thrombosis, and endothelial proliferation in the meninges, cerebral cortex, and corpus striatum. The condition is a rheumatic meningoencephalitis.

The *visceral vessels* may show peculiar and characteristic lesions which are described in Chapter XVI.

*Rheumatic Pneumonia.*—Patients dying in the acute stage may show pneumonic consolidation, the lung having a peculiar India rubber consistence. There may be true Aschoff nodules in the fibrous septa, an interstitial infiltration of large, often multinucleated, cells, or areas of acute focal necrosis. (Gouley and Eiman.) *Pleural lesions* have been described. In many of the fatal cases there is a pleurisy, at first dry and later with effusion. There is metaplasia of the endothelium and inflammation in the subpleural layers.

*Rheumatic peritonitis* occasionally occurs. Rhea found plaques of inflammation on the parietal peritoneum and nodules in the subperitoneal connective tissue in a case of rheumatic carditis. The microscopic picture was identical with that in the heart except that the lesions were diffuse rather than focal.

## PNEUMOCOCCAL INFECTIONS

The *Diplococcus pneumoniae* or pneumococcus is a lance-shaped Gram-positive diplococcus, which shows a well-defined capsule when it grows in the body. In fluid media and in the sputum it may grow in chains. It can be differentiated from the streptococcus by its ready solubility in bile and by the fact that it ferments inulin. Its virulence is soon lost when grown on culture media but can be recovered by animal passage.

A number of different groups can be distinguished by means of specific antisera. This can be done most conveniently by Neufeld's "Quellung" (swelling) reaction, in which the specific antiserum causes swelling of the capsule of pneumococci of the same type. (Fig 59.) In cases of lobar pneumonia Type I accounts for about 35 per cent, Type II for 25 per cent, Type III for 10 per cent, and Type IV (a heterogeneous collection of subtypes) for 30 per cent. Type III is the most virulent; it produces a slimy growth in culture, and gives rise to a characteristic mucoid glairy exudate. The typing of pneumococci has lost much of its significance since the introduction of sulphonamide therapy.

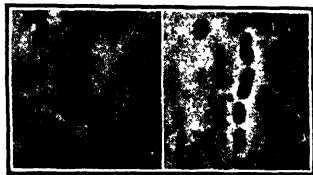


FIG. 59.—Typing of pneumococci. A, positive reaction.  $\times 2200$ . B, negative.  $\times 2400$ .

The principal disease caused by the pneumococcus is lobar pneumonia. This is described in connection with diseases of the lungs. The pneumococcus is a pyogenic organism, but it also has a marked ability to excite the formation of fibrin. The pulmonary alveoli are therefore filled with an inflammatory exudate composed mainly of pus cells and fibrin. Pleurisy is an invariable and empyema a less common accompaniment of lobar pneumonia.

Other lesions caused by pneumococci are endocarditis, pericarditis, peritonitis (especially in children), arthritis, meningitis, middle-ear suppuration, infection of the nasal sinuses, etc. These conditions will be described in their proper place.

### BACILLUS TYPHOSUS INFECTION

*Bacillus typhosus* is identical morphologically with *Bacillus coli*. It is Gram-negative and actively motile. The two organisms can readily be distinguished by their reaction on lactose in the presence of an indicator. *Bacillus coli* ferments the sugar with the formation of acid which changes the color of the indicator; *Bacillus typhosus* has no action on lactose, it is a non-lactose fermenter, so that the color remains unchanged. The same is true of the paratyphoid bacilli, which behave in the same way and produce the same lesions as the typhoid bacillus, so that they may be considered together. The final proof of the identity of a member of this group is afforded by producing agglutination of the bacilli by a specific antiserum in high dilution.

**Infection.**—The source of fresh infection is always human, either a patient suffering from the disease or a healthy carrier. The infection is alimentary, and is conveyed by infected water, milk or food, or by direct contagion. Epidemics can usually be traced to either water or milk infection. The bacilli do not multiply to any degree in water, but they multiply rapidly in milk, so that a milk-borne epidemic is more violent and explosive due to the massive infection. Food and milk may be infected by the contaminated fingers of a carrier (cook, dairy-man) or of a nurse who has been looking after a typhoid patient. Flies may convey the infection from uncovered dejecta to uncovered food. Water infection is usually due to sewage contamination.

One of the chief sources of danger is the *chronic carrier*. A patient who recovers from the disease may continue to harbor the bacilli in his body, which are discharged for years usually in the stools, sometimes in the urine. A carrier is only dangerous when his occupation entails the handling of food or milk or if the excreta are not properly disposed of (camp life, armies in the field, etc.).

The portal of entry is usually supposed to be the lymphoid tissue of the small intestine where the earliest lesions occur, but there has always been a wide gap in our knowledge between the entry of the bacilli into the mouth and the development of symptoms of infection. It is impossible to see typhoid bacilli in any numbers in the lesions, except when a considerable interval has elapsed between death and

autopsy, and yet they can usually be demonstrated by cultural methods. Goodpasture has shown that in early stages of the disease small Gram-negative bacilli, which appear to be typhoid bacilli, can be seen in large numbers in the cytoplasm of young plasma cells in the lymphoid follicles of the ileum, and he suggests that the young plasma cell acts as an essential cellular host for the bacilli which multiply within it. The abdominal lymph nodes draining the bowel are infected from the beginning and give a pure culture of the bacillus. The bacilli multiply in the lymph nodes during the period of incubation; they then pass by the thoracic duct to the blood stream and are liberated into the blood stream at the end of the incubation period; many of them are broken down and their endotoxins liberated. It is these toxins which cause the general symptoms and some of the lesions (focal necrosis of liver, Zenker's degeneration of muscle).

**Symptoms.**—The symptoms are partly general, partly intestinal, partly hemopoietic. The general symptoms are fever, headache, malaise, lethargy, and a clouding of the mind which gives the name to the disease (*typhos*, a cloud). These symptoms are a manifestation of toxemia due to the action of bacteriolysis on the bacilli; they therefore become more pronounced as the disease progresses. Rose spots appear on the abdominal wall. Bronchitis and nose-bleeds may be early symptoms. The intestinal symptoms are abdominal discomfort, constipation or diarrhea. The hemopoietic symptoms are enlargement of the spleen, leucopenia, and disappearance of the polymorphonuclear leucocytes and eosinophils. I do not know if this is true of other localities, but the clinical picture as seen in Winnipeg and in the province of Manitoba has altered considerably, the classical text-book picture is seldom seen, and diagnosis has become more difficult. The laboratory aids to diagnosis, and in particular the Widal test, seem to be much less reliable than formerly.

**Lesions.**—Typhoid fever is primarily an infection of the hemopoietic tissue, and in particular the lymphoid tissue of the intestine, the abdominal lymph nodes, the spleen, and the bone-marrow. As there is always a bacteremia any organ may be involved, but the most important lesion to add to the above is infection of the gall-bladder. The typhoid bacillus excites a peculiar cellular reaction which is quite characteristic, and unlike the suppurative reaction produced by its pyogenic cousins, the colon bacillus and the dysentery bacillus. There is an almost complete absence of polymorphonuclear leucocytes, their place being taken by large mononuclear phagocytes of the reticulo-endothelial system.



FIG. 60.—The lesion of typhoid fever; a collection of large mononuclear cells.  $\times 600$ .

(Fig. 60.) These phagocytes may contain lymphocytes, red blood cells, and other cell inclusions. (Fig 61.) The lesion is productive rather than exudative in type. The red marrow is filled with these cells, to



FIG. 61.—Typhoid macrophages. The one in the center contains a lymphocyte and four erythrocytes.  $\times 1000$ .

the exclusion of the polymorphonuclear and eosinophil leucocytes, thus explaining the leucopenia and the disappearance of polymorphonuclears and eosinophils.



FIG. 62.—Typhoid ulcers of the bowel. A necrotic slough occupies the center of each lesion.

The *intestinal lesions*, which are confined to the lymphoid tissue, are most marked in the lower part of the ileum, but may involve the greater part of the small intestine and also the colon. The Peyer's patches and the solitary follicles are crowded with the large mononu-



clear phagocytes, so that the lymphoid masses project above the surface. By the end of the first week these lesions become necrotic, the overlying mucosa forms a slough, and when this separates it leaves an ulcer. (Fig. 62.) The ulcers are round or irregularly oval with the long axis in the long axis of the bowel, since that is the direction of the Peyer's patches. In the cecum and colon the ulcers are smaller, owing to the smaller size of the solitary follicles. Many are quite shallow, but the submucosa is often perforated, so that the floor of the ulcer is formed by the muscularis or even the peritoneum. There may be no ulcers, for the patient may die of toxemia before ulceration has time to take place. The number and size of the ulcers bear no relation to the severity of the disease. But the ulcers are accountable for the two complications which are responsible for a majority of the deaths, namely, hemorrhage and perforation. As the patient may have a deep ulcer and yet be only slightly ill, it follows that every case of typhoid must be treated with the greatest care. The ulcers heal with the formation of little or no scar tissue. The ulcer is covered by a simple type of epithelium without the formation of new glands.

The *lymph nodes* of the mesentery are always involved, especially those which drain the lower ileum. Their sinuses are distended with large mononuclear phagocytes, and the nodes are therefore swollen and soft.

The *spleen* shows acute splenic swelling. It is moderately enlarged, usually weighing about 500 grams, deep red in color and very soft. Microscopically the usual collections of large mononuclear cells are seen with small areas of necrosis, but the most striking lesion is a crowding of the pulp with enormous numbers of red blood cells, so that it may seem to contain little but blood. The reason for this extreme congestion is not clear, for it is not seen in the other lesions; possibly the masses of mononuclears obstruct the outflow from the sinuses so that they become overfilled with blood.

In the *liver* the typhoid lesion is focal necrosis. The lesion is really a combination of mononuclear proliferation and necrosis. The large mononuclears block the sinusoids and the liver cells become necrosed. The lesions are quite small and resemble miliary tubercles.

The *gall-bladder* is always affected, and this is really one of the most important lesions, although the structural change is negligible. The bacilli reach the gall-bladder very early indeed, by way of the blood stream. Gay has shown that when typhoid bacilli are injected into the vein of a rabbit they can be recovered from the gall-bladder within one-half hour. The bacilli grow readily in bile and pass into the feces. Cultures of the intestinal tract show that the bacilli are most numerous in the duodenum, and steadily diminish from above down. Most of the bacilli in the stools are therefore derived from the gall-bladder and not from the ulcers in the bowel. The bacilli multiply in the gall-bladder, so that far more are found in the stool in the third than in the first week. The bacilli may continue to live in the gall-bladder after recovery and are passed in the stools; such a person is a

chronic carrier, for the bacilli are still virulent. The Widal test is usually positive. Bacilli can be demonstrated in the wall of the gall-bladder during the disease, but any inflammatory lesions are very slight. The disease seems to predispose to the formation of gall-stones, which may contain living bacilli many years after the original infection. In carriers the mucosa is infiltrated with lymphocytes and contains many lymph nodes with germinal centers (Mallory and Lawson).

The *kidneys* show cloudy swelling and clumps of bacilli, so that bacilli often appear in the urine. A urinary carrier continues to discharge bacilli long after recovery.

The *lungs* may show bronchitis in the early stage and pneumonia (lobar or bronchopneumonic) later. The pneumonia is usually pneumococcal, but it is sometimes due to the typhoid bacillus.

The *heart* muscle is soft and swollen, and the blood-pressure low. The pulse is characteristically slow, and the pulse often dicrotic.

The *veins* are often thrombosed, especially the femoral and saphenous veins and the cerebral sinuses.

The *muscles* may show Zenker's degeneration, a hyaline change in which the fibers lose their transverse striations and are broken up into swollen hyaline masses. The chief sites are the lower part of the rectus abdominis, the diaphragm, and the thigh muscles. Rupture of the muscle may occur with hemorrhage. The condition, which is due to the toxins, may also occur in other infections. (Fig. 12, page 38.)

The *bones* may show a chronic suppurative lesion, either abscess or periostitis, which may come on months or years later. The common sites are the tibia, sternum, ribs, and spine. The pus often contains living typhoid bacilli.

The *blood* shows a marked leucopenia (2000 to 5000 per c.mm.), with decrease in the polymorphonuclears and eosinophils (these may vanish) and an increase of large mononuclear cells.

**The Relation of Symptoms to Lesions.**—The general symptoms such as fever, headache, lethargy are due to the toxins which are liberated when the bacilli are broken down in the blood stream. The rose spots are caused by bacterial emboli in the skin capillaries. The enlargement of the spleen which forms one of the chief clinical pictures is due to the great accumulation of cells in the splenic pulp. The intestinal symptoms including hemorrhage and perforation are the result of the ulcers. The blood changes (leucopenia, disappearance of polymorphonuclears and eosinophils) are the direct result of the lesions in the bone-marrow. The carrier state is an indication that the constant infection of the gall-bladder has become chronic instead of clearing up.

**Laboratory Aids in Diagnosis.**—The four most valuable laboratory tests are: (1) blood culture, (2) the Widal test, (3) the demonstration of bacilli in the feces and the urine, and (4) the leucocyte count. *Blood culture* is positive at the beginning of the disease (the period of bacteremia) and during the first week. After that more and more bacilli are destroyed so that it becomes

increasingly difficult to get a positive culture. The *Widal test* has a great reputation, but it has very real limitations and is less valuable now than formerly for the two reasons that many persons who have been inoculated against typhoid give a positive agglutination reaction, and many cases of typhoid do not give a reaction until late in the disease, by which time the diagnosis is self-evident. After recovery the agglutinins persist for months, sometimes for years, while the agglutinins due to inoculation usually disappear in a few months, although they may reappear after a number of years as the result of some non-typhoid disease (*anamnestic reaction*). The *Widal test* is frequently negative in carriers. *Bacilli in the stools* are found more readily in carriers than in the active disease. They are most numerous in the third week, as by that time the bile is loaded with bacilli. The *urine* may contain bacilli in the third week. The *dialo reaction* in the urine is negatively pathognomonic, as it is present in practically every case, but is also found in other infective fevers, especially military tuberculosis, which may simulate typhoid. Culture of the *bile* obtained by *duodenal drainage* is one of the best methods of detecting a carrier. The peculiarities of the *leucocyte count* have already been described. For making an early diagnosis the two most valuable tests are blood culture and the leucocyte count.

### TUBERCULOSIS

Tuberculosis is a chronic inflammation caused by the tubercle bacillus. It belongs to the group of the *infectious granulomata*, other members of which are syphilis, leprosy, actinomycosis, and other less common infections. The original meaning of the word was a new formation resembling granulation tissue. The resemblance to granulation tissue is fancied rather than real. A granuloma is an inflammatory mass consisting largely of epithelioid cells, as in tuberculosis, or of lymphocytes and plasma cells, as in syphilis, whilst in actinomycosis an added suppuration complicates the picture. The variations of tuberculosis are endless but they are merely the result of the interplay of the forces of destruction and repair. In man the tendency to repair is commonly greater than the destructive process, especially if the affected part such as the lung can be put at rest. Even though destruction may have proceeded for some time it may be followed by a remarkable degree of repair, so that in tuberculosis it cannot be said that "the struggle naught availeth, the labor and the wounds are vain." In this struggle the three factors to be considered are size, of dose, immunity and allergy. Virulence of the bacilli might be added, but this does not appear to play an important part.

The disease is amazingly widespread, as is shown both by the tuberculin reaction and autopsy examination. The figures naturally vary in different countries, and the incidence is higher in large cities than in rural districts. Statistics compiled from the great centers and from the poorer classes of the community show that before the age of ten about 15 per cent, before the age of twenty from 30 to 60 per cent, and after middle life about 99 per cent of persons are infected. These figures were compiled from autopsy studies in the earlier part of this century. As a result of the campaign against tuberculosis a generation of children and young adults has grown up which has escaped primary infection and is negative to tuberculin. Thus in a school for nursing at Oslo 52 per cent of the entering students were tuberculin-

negative (Heimbeck). This has produced a great change in the disease picture.

**The Tubercle Bacillus.**—The *Bacillus tuberculosis*, discovered by Koch in 1882, is a thin, curved rod, sometimes beaded, staining with difficulty and growing in artificial culture with still greater difficulty. Koch's discovery is one of the masterpieces of bacteriology. In the course of one year he found it, invented a culture medium on which it could be grown, and reproduced the disease in animals. It can be recognized by its acid-fast character. The bacillus is a strict *aëro*b, growing best in an abundant supply of oxygen. This may explain the fact that the lung is by far the most important site of tuberculosis. It is important to remember that many saprophytic non-pathogenic acid-fast bacilli occur in Nature, *e. g.*, in hay, butter and milk, and others may occur in man apart from tuberculosis, in the sputum, saliva and smegma. A rapid method of demonstrating the bacilli in sections of tissue is by the use of fluorescent dyes and the fluorescent microscope. The bacilli appear as bright rods on a dark background, and can be seen without an oil-immersion lens, so that a wider field can be covered.

Chemical analysis has shown that the tubercle bacillus consists of a number of fractions, of which a protein, a polysaccharide and a lipid (phosphatide) seem to be the most important. The lipid is responsible for the acid-fastness, and for the most characteristic element in the cellular reaction, the epithelioid cell. Dead bacilli can therefore produce typical tuberculous lesions characterized by typical cellular reactions and necrosis. Moreover when the lipid is extracted and injected it causes similar changes. It is on the protein fraction that the allergic response depends, and tuberculin, which is a glycerin extract of tubercle bacilli, consists largely of this fraction. The significance of these facts will become evident as we proceed.

The bacilli can be demonstrated in three ways: by staining a smear or section, by inoculating a guinea-pig, and by culture. (1) The staining method is the most commonly used for sputum examination, but 100,000 bacilli per cc. must be present if they are to be detected by this method. (2) Guinea-pig inoculation is 1000 times more sensitive, but the long delay (a month or more) is a great disadvantage. Feldman has shown that a quicker result is obtained by injecting the material into the brain. (3) Various methods of culture have been used (potato medium, etc.), the results corresponding closely to animal inoculation both as regards reliability and time consumed. In 1946 Dubos introduced the use of a commercial detergent, a water soluble lipid (Tween 80), added to some of the common fluid media. This has revolutionized the rate of growth, positive cultures being now obtained in from eleven to fifteen days.

In human pathology two forms of tubercle bacilli are important, the *human* and *bovine*; perhaps a third should be added, the *avian*. The bone type is likely to be met with in children owing to the larger consumption of milk, the human form in the adult. The two varieties of bacilli cannot be distinguished with certainty under the microscope, but can readily be differentiated by culture and animal inoculation. On glycerin agar the human type grows readily, the bovine type does not. On the other hand, the bovine type will produce a fatal general tuberculosis when injected into a rabbit or calf, whereas the same dose of human tubercle bacilli will only cause a local lesion. The percentage of the bovine type of infection varies much in different countries. The bovine bacillus plays a very small part in pulmonary tuberculosis. For practical purposes it may be said that every adult case is human in type, although a number of cases of bovine infection have been recorded. Blacklock, in an investigation of childhood tuberculosis in Glasgow where the bovine form of infection is quite prevalent, found that all the pulmonary cases were of the human type.

**The Inflammatory Reaction.**—The reaction of the body to the tubercle bacillus varies considerably, depending on the following fac-

tors: (1) the species of animals, (2) the size of dose, (3) the question of whether the animal is tuberculosis-free or has already been infected. The influence of these factors will be discussed as we proceed. In spite of possible variations there is a standard type of reaction caused by a moderate dose of bacilli of unattenuated virulence in a susceptible species of animal which is infected for the first time. *Polymorphonuclear leucocytes* are the first to arrive in response to an injection of tubercle bacilli. They are actively phagocytic, but are unable to damage the bacilli which they engulf. They play a useful part, however, in focalizing the infection by preventing to some extent the drift of bacilli through the tissues. The response of the polymorphonuclears is very much more marked in a reinfection, i. e., in the allergic inflammation of an already tuberculous animal. Their appearance is transitory, and within twenty-four hours they are replaced by *mononuclear cells*, also known as macrophages and monocytes.

These cells represent the essential reaction of the body to the tubercle bacillus, but it is to the fatty envelope of the bacillus that the response is made, for the same effect is obtained by the injection of lipoid extracted from the bodies of the bacilli. In some of the experimental work they have been the first cells to arrive. Thus Fried found that the intratracheal injection of bacilli in the rabbit caused an amazingly rapid appearance of mononuclears. When the animal was killed one minute after the injection the cells had begun to appear and in the course of five minutes a definite primitive tubercle had been formed within the alveoli. The mononuclears are highly phagocytic members of the reticulo-endothelial system. It appears probable that they have a dual origin. In the liver and lung they arise from the histiocytes or fixed cells of the system (Kupffer cells, alveolar phagocytes), while in the omentum they appear to be derived from the monocytes of the blood. The bacilli and also the polymorphonuclears containing bacilli are phagocytosed by the mononuclears, by which they are gradually broken down with dispersion of the lipoid throughout the cytoplasm. This dispersion results in the transformation of the mononuclear into the *epithelioid cell* (epithelial-like), which is the most characteristic single feature of the tuberculous reaction. It is a large, pale cell with rather indistinct margins, the nucleus is large and vesicular, and the abundant cytoplasm often presents processes which pass from one cell to another to form an epithelioid reticulum. The epithelioid cell, then, may be regarded as a large mononuclear which has partially digested tubercle bacilli, and its distinctive cytoplasmic state seems to be the result of destruction of many bacilli with progressive emulsification of their lipoid (Long, Lurie). The epithelioid cell is particularly rich in ascorbic acid (vitamin C), and it seems probable that this substance is connected with the enzyme activity of the principal reactive cells. The lymphocytes of the tubercle do not contain any demonstrable ascorbic acid. It is evident that by the time the mononuclears have become transformed into epithelioid cells the bacilli have undergone extensive destruction. This explains the difficulty

which is experienced in demonstrating bacilli in the ordinary type of lesion in man, in which they are few and far between and may only be found after prolonged search, although in acute fulminating lesions such as tuberculous caseous pneumonia they may be present in great numbers. The mononuclears do not always have the power of destroying the bacilli which they engulf. Thus in the rat the bacilli thrive and multiply within the phagocytes, and the latter also multiply with the remorselessness of a malignant growth, until finally the animal succumbs to the cellular accumulation.

Giant cells are formed by fusion of a number of epithelioid cells. They may attain a great size, and contain large numbers of nuclei, usually arranged either around the periphery or at one or both poles, but occasionally scattered through the cytoplasm. Medlar points out that the matrix of the cell is necrotic (caseous) from the beginning, and suggests that the peculiar arrangement of the nuclei at the periphery is due to the epithelioid cells surrounding a central piece of necrotic material. Giant cells are not formed until necrosis has occurred. They are found in small caseous areas or at the edge of larger areas. They often contain tubercle bacilli, and their function is to digest and remove dead tissue. They are foreign body giant cells, and indicate that an active resistance is going on. Giant cells are very characteristic of tuberculosis, but they occur in other chronic inflammations (syphilis, actinomycosis), and they may be absent in the acuter forms of tuberculosis where resistance is low (tuberculous meningitis, etc.), and in very low-grade infections where there is no necrosis.

By the end of a week lymphocytes appear, and form a ring around the periphery of the lesion. They are small cells with dark nuclei, identical with the lymphocytes of the blood, but they are probably derived from the cells of the perivascular lymph sheath or other lymphoid structures. Lymphocytes probably play an important rôle in the resistance of the body to tubercle bacilli. The protective action seems to be due to the lymphocytes disposing of the bacterial toxins rather than to a direct action of the bacilli. It is well-known that tubercle bacilli grow more readily in lymphoid tissue than elsewhere, indicating that the lymphocytes are unable to inhibit the growth of the bacilli.

The small mass of newly-formed or newly-arrived cells constitutes a tiny translucent nodule visible to the naked eye and known as a *tubercle* or *miliary tubercle* (Fig. 63), since it is at first about the size of a millet seed, although it increases in size and several tubercles may fuse to form a larger mass. It is avascular, so that when the vessels of a tuberculous organ such as the lung are injected with a colored medium the tubercles stand out unstained. By the end of the second week caseation begins. This is a form of coagulation necrosis caused by the bacterial toxins, and the intensity of the necrosis varies with the size of dose. Massive infection is likely to be accompanied by extensive caseation, as in acute tuberculous pneumonia. In the center of the tubercle the cells lose their outline, the nuclei disappear, and

all structure is lost. (Fig. 64.) In the caseation of a syphilitic gumma the loss of structure may not be so complete, and some of the original outline may still be dimly discerned. Other respects in which the two



FIG. 63. —A miliary tubercle in the lung, showing epithelioid cells, giant cells, and peripheral lymphocytes.  $\times 150$ .

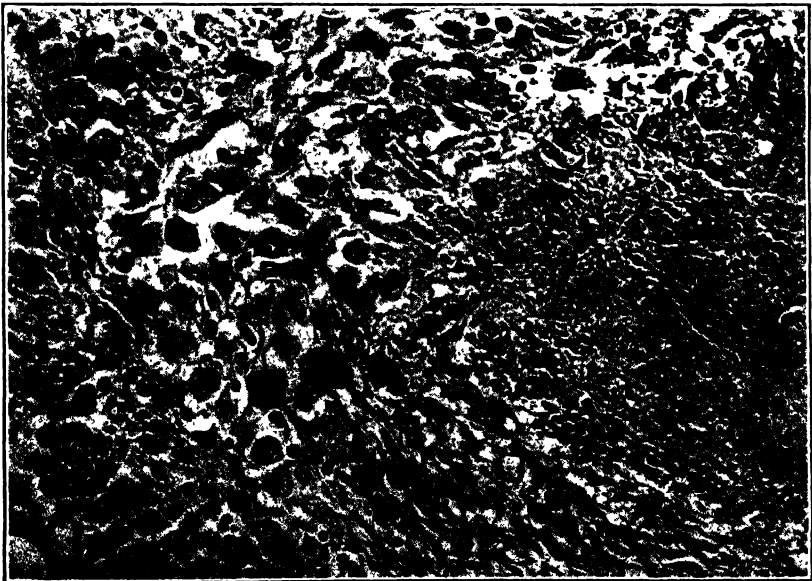


FIG. 64. —Tuberculous caseation, showing destruction of epithelioid cells.  $\times 325$ .

lesions may differ will be considered in connection with the gumma. The tubercle now presents a homogenous center staining red with eosin, a periphery of pale epithelioid cells with one or more giant cells, and an outer zone of dark blue lymphocytes. Caseation is not always present. It is absent in the hyperplastic form where the virulence of the bacillus is low or the resistance high.

There is a tendency for caseation to be followed by *softening* and liquefaction. Long points out that softening of the caseous tubercles is the key problem in tuberculosis, for were it not for softening the disease would be self-limited. Softening is associated with an extraordinary multiplication of the bacilli, so that when liquefied material is first discharged into a bronchus it has its maximum infecting power. From this it follows that acute fresh cavities discharging soft yellow lumps in the sputum are highly infective, while old chronic cavities are not an important source of infection. The precise cause of the softening is not understood.

The *future history of the tubercle* varies greatly. (1) The experimental tubercle may resolve, disappear completely, and leave no trace. It is difficult to know if this occurs in man, but it probably does. The peritoneum may be found studded with tubercles, and yet if the abdomen is opened a year later the membrane may be smooth and normal. (2) A very common occurrence is for the caseous area to be surrounded by fibroblasts which form a fibrous capsule for the tubercle. Lime salts are deposited, and the calcified tubercle is said to be *healed*, but even in this quiescent lesion living bacilli may still lurk and can be demonstrated by animal inoculation. Reticulum may be present in tubercles composed entirely of epithelioid cells, and as reticulum is formed before connective tissue it is possible that the one may develop into the other, and that the mononuclears may take some part in the formation of collagen. (3) There may be a low-grade inflammation with the formation of *tuberculous granulation tissue* with many tubercles but no caseation. This is due to low virulence or high resistance. This hyperplastic form is seen in the synovial membrane of joints, in the cecum, and occasionally in lymph nodes. (4) There may be *spread* of the infection, the bacilli being carried by phagocytes through the tissues, giving rise to the formation of new tubercles which fuse together until large caseous areas are formed. (5) There may be an *acute inflammatory reaction* when the infection is virulent or massive, as seen in tuberculous meningitis and acute tuberculous pneumonia.

This reaction, in place of being mainly productive, is essentially exudative in type and is characterized by a great outpouring of polymorphonuclear leucocytes and serum with, it may be, an abundant formation of fibrin. It is, however, not in first infections but in reinfections, sometimes called secondary infections, that the acute inflammatory reaction is seen to best advantage, and we may now turn to a consideration of the lesions which develop in the already tuberculous or allergic animal or man.



**Allergy and Immunity in Tuberculosis.**—Robert Koch realized the fundamental distinction between the reaction to the tubercle bacillus in a healthy animal and in one already infected with tuberculosis. If a healthy guinea-pig is inoculated with tubercle bacilli of low virulence a nodule forms by the end of two weeks. This breaks down and never heals, for the guinea-pig, in contradistinction to man, has no natural immunity. The regional lymph nodes become enlarged and caseous, as the bacilli are not retained at the site of inoculation. These tuberculous nodes form a valuable indication of the site of the primary infection. Involvement of the cervical nodes points to the tonsil as the portal of entry, the tracheo-bronchial nodes to the lung, the mesenteric nodes to the intestine. Swelling of the regional nodes is followed by general infection of the guinea-pig and death in two or three months.

The sequence of events following the inoculation of an animal which has previously been infected (reinfection) is very different. If a second dose is given a couple of weeks after the first, a local swelling appears in a few days; this breaks down and forms an ulcer, but the ulcer soon heals, and the regional lymph nodes are not enlarged (Koch phenomenon). This does not mean to say that they are not infected, for tubercles can be found in the nodes both in the experimental animal and in human reinfection, but most of the bacilli are retained at the site of inoculation, and those which succeed in reaching other parts find the soil unfavorable. The local reaction is an acute inflammatory one, it is more prompt in its appearance than in the healthy animal, and it is characterized by marked outpouring of polymorphonuclear leucocytes and plasma and above all by the occurrence of massive necrosis. It will be recognized that this reaction, which can be elicited by the injection of dead bacilli and tuberculin as well as by active infection, is a manifestation of the allergic inflammation which has already been studied in the previous chapter. It is dependent on the fact that the relatively bland tuberculoprotein acts in the allergic body as a powerful irritant and necrotizing poison.

It has long been supposed that it is due to the protective action of this allergic inflammation that the lesion of reinfection in the now hypersensitive animal is more localized and that the regional lymph nodes are not massively involved. No clear distinction was drawn between allergy and immunity in tuberculosis, and the fact that the allergic animal enjoyed the benefits of protection was attributed to the allergic local reaction. A local sacrifice of tissue was regarded as the necessary price to be paid for protection of the rest of the body. Rich believes that allergy and immunity in tuberculosis are two entirely distinct entities, and that one can be destroyed without affecting the other. Both states develop as the result of infection, but they represent the response of the body to different elements in the tubercle bacillus, so that immunity is not achieved through allergy. In opposition to the views of Rich is the work of Willis and Woodruff, who infected guinea-pigs some of which were allergic and some had been desensitized. In

the desensitized animals there was an overwhelming growth of tubercle bacilli compared with growth in the allergic animals.

The response to tuberculin is an allergic one. Tuberculin allergy may disappear after healing of a tuberculous lesion, although sensitivity is never lost in presence of active infection. Children often change from a positive to a negative tuberculin reaction, but this rarely happens in adults.

The distinction between primary and secondary infection can be seen in the lungs. Using the regional lymph node involvement as an indicator of the primary lesion, Ghon was able by careful dissection to demonstrate a primary lung lesion in over 90 per cent of children. This lesion, often called the *Ghon lesion* (Fig. 65), is a small caseous



FIG. 65.—Active Ghon lesion. There is a subpleural caseous lesion in the lower lobe. The lymph nodes at the hilus are enlarged and caseous. Miliary tubercles are scattered through the lung, especially in the lower lobe. Some of the upper lobe has been removed. Death was due to general miliary tuberculosis.

focus not more than 1 cm. in diameter, usually single, and situated in any part of the lung, but generally just under the pleura, and limited by a fibrous capsule. There is a larger caseous focus in the lymph nodes draining this area. It is of interest to note that Ghon's work was published in 1912 but the lesion known by his name was described in every detail in 1898 by a Paris physician, George Küss, who wrote a monograph on the subject which has been completely neglected. Very many of these lesions are healed, not only calcified but ossified. These lesions seldom contain viable tubercle bacilli, as shown by culture and guinea-pig inoculation (Feldman and Baggens-toss). The lesion may be healed, and yet the histological picture (cellular infiltration)

may suggest active infection owing to the frequent presence of silica. If healing does not occur the child becomes allergic, the caseous lesions break down, and a rapidly spreading tuberculous pneumonia is apt to develop. The younger the child the greater is the danger, for he has not had time to become immunized by repeated minimal infections. Therefore tuberculosis is especially dangerous in the first year of life. The child with primary infection either recovers or dies; he does not develop the chronic thick-walled cavities so characteristic of the disease in the adult.

Opie has shown by means of roentgen-ray pictures of the lungs re-

moved from the body at autopsy that two types of healed calcified lesion can be distinguished. In the one there is a focal lesion which may be in any part of the lung and is associated with caseous or calcified lymph nodes indicating a primary infection; in the other there is an apical lesion with the character of a second infection and no involvement of the regional lymph nodes. The first type is found in children and persists in adults; the second type occurs in adults.

A period of latency separates the primary and secondary types. The years from four to fourteen are almost free from fatal pulmonary tuberculosis.

When an adult develops tuberculosis he has already been infected in childhood. The one lesion is not a development of the other, but the result of a fresh infection from without massive enough to break down the immunity produced by the primary lesion. As the adult lesion is of the secondary type it will become caseous and break down with the formation of a cavity. If the immunity due to the primary lesion has disappeared, reinfection will be of the nature of a first infection, and the patient may die of acute tuberculous pneumonia as in the first year of life. Owing to the greatly decreased incidence of childhood tuberculosis, primary tuberculosis in the adult is becoming increasingly common. The majority of persons infected for the first time in young adult life show few symptoms or serious effects, the disease being detected by routine tuberculin tests followed by roentgen-ray examination. If exposed a second time to infection, the patient will develop the usual lesions and symptoms of reinfection.

It is evident that immunity is the master word in tuberculosis. It is more to be desired than freedom from infection, for the latter is an unattainable ideal, and the rarer the infection the more dangerous does it become.

**Method of Infection.**—It is easy to infect a susceptible animal by three routes: inoculation, inhalation, and ingestion. In man we are interested not in possible routes, but in the method of common occurrence. Unless this is known prevention is not possible.

1. **Congenital Infection.**—This may occur through the placenta, and tubercle bacilli have been found in the mesenteric lymph nodes of the newborn. It is so rare as to be negligible.

2. **Infection Through the Skin.**—This is the chief method of infection in the experimental animal, but in man it is of little importance. A tuberculous lesion may develop on the hand of a nurse, surgeon, or pathologist (*verruca necrogenica*) through handling infected material. The infection may spread to the regional lymph nodes, but seldom gives rise to general tuberculosis.

3. **Infection Through the Gastro-intestinal Tract.**—This is the route through which children are infected by drinking tuberculous milk. In children at least 60 per cent of the cases of abdominal tuberculosis are due to the bovine type of bacillus. Most of the cases of cervical lymph node tuberculosis in children are bovine in type, the bacilli entering by way of the tonsils. On the other hand, pulmonary tuber-

culosis in the adult is never bovine in type and very rarely in children. The lungs are therefore not infected through the gastro-intestinal tract.

**4. Infection by Inhalation.**—This is the route by which the lungs are infected. There are three ways in which tubercle bacilli may be inhaled into the lungs.

1. *Dust Infection.*—Infected sputum when it dries may become converted into dust, and the bacilli are inhaled with the dust. It is hard to say how frequent this method is. The bacilli are readily killed by sunlight, though they may survive a long time in the dark, so that most of the dust in the street can only be slightly infective. Moreover, only minimal doses are likely to be inhaled in this way, and such doses are more likely to induce immunity than to break down infection and cause serious disease. But if a person lives in the same house as a patient with pulmonary tuberculosis who expectorates on the floor there is great danger of infection.

2. *Droplet Infection.*—When a patient with pulmonary tuberculosis coughs he infects the air in his immediate neighborhood with millions of tubercle bacilli contained in tiny drops of moisture. Exposure to a patient who takes no precautions when coughing may be followed by the massive infection which is so important in breaking down resistance. This is probably the chief method of infection in the adult.

3. *Mouth Infection.*—Bacteria, *e. g.*, *Bacillus prodigiosus*, when placed in the mouth of an animal can be demonstrated in the lungs in a few minutes; they appear to have been inhaled in minute droplets of fluid. It is probable that many children acquire the human type of infection through introduction of bacilli into the mouth by contaminated hands followed by inhalation, for infection is commonest at a period (three to six years of age) when the child is most in the open air and least likely to be infected by the first two methods.

**Method of Spread.**—The tubercle bacillus is non-motile, but it can be transported in the bodies of phagocytic cells. There are four chief methods of spread:

1. **By Direct Extension.**—The phagocytes carry the bacilli into the lymph spaces of the surrounding tissue. More and more tissue becomes necrotic, until the caseous area may become very large.

2. **By the Natural Passages.**—The infection shows a tendency to pass along a tube, which is never seen in syphilis. It may spread from the kidney down the ureter to the bladder, from the testicle along the vas deferens to the prostate, from one part of the lung to another by the bronchi. This spread may be in the submucous coat of the tube or inside the lumen, *i. e.*, sputum coughed up one bronchus and inhaled into another.

3. **By the Lymphatics.**—Tuberculosis is primarily an infection of lymphoid tissue. The bacillus may be detained by the lymph follicles of the mucosa (pharynx, bronchi, intestine) or by the regional lymph nodes. If it succeeds in passing the Scylla of the lymph follicles and the Charybdis of the lymph nodes, it sets out upon an Odyssey which may carry it far, but always toward the lungs. If it enters the thoracic

duct it gains the venous blood stream and reaches the lungs. Here it may be arrested and may set up a focus of disease and infect the bronchial lymph nodes, or it may run the gauntlet of the pulmonary capillaries, enter the general circulation, and reach any organ in the body.

Krause has shown that in the experimental animal this dissemination may be remarkably rapid. He injected virulent bacilli under the skin of a guinea-pig, and found the bacilli in every part of the body in the space of four days, long before the appearance of the local lesion. When the inoculated area was excised at the end of an hour it was already too late. It must be remembered that the guinea-pig is a highly susceptible animal, and that these results cannot be applied unreservedly to man in whom resistance is comparatively high. We shall see, however, that syphilis shows just the same rapid dissemination from the primary seat of infection long before a local lesion has had time to appear.

**4. By the Blood Stream.**— From what has just been said it is evident that *tuberculous bacillemia* is a common if not an invariable accompaniment of tuberculous infection. The bacilli have been demonstrated in the blood by means of suitable technique in cases of active tuberculosis. There is a good deal of difference of opinion at present as to how frequently this can be done. Löwenstein and his associates have published startling statistics claiming that the bacilli can be cultivated from the blood in the majority of cases of tuberculosis, even in such localized forms as tuberculosis of the eye, skin and kidney. Positive findings have also been reported in chorea, rheumatic fever, and multiple sclerosis. In a critical analysis of these results, Wilson points out that acid-fast bacilli are occasionally present in commercial distilled water, tap water, dust, etc., and considers from the results of animal inoculation that the percentage of positives in severe pulmonary tuberculosis is 5 to 10 per cent, in miliary and meningeal tuberculosis it is 30 to 40 per cent, and only 2 per cent in cases of non-pulmonary tuberculosis. A bacillemia must be distinguished from the condition known as *general miliary tuberculosis*. Here enormous numbers of bacilli are poured into the blood stream. It used to be thought, following the teaching of Weigert, that this massive infection was the result of a tuberculous focus ulcerating through the wall of a vein. It seems probable, however that the correct explanation is drainage of tubercle bacilli from an active extrapulmonary tuberculous focus (bone, kidney, etc.), or a primary focus in the lung by the lymphatics into the venous system (Auerbach). The result is an acute toxic infection which may terminate in death in the course of a few weeks. Tiny miliary tubercles are found in every organ of the body, though these may hardly be visible to the naked eye. It is a mistake, however, to think that miliary tuberculosis must be acutely fatal. *Chronic miliary tuberculosis* is compatible with years of life and with recovery (Hoyle and Vaizey). The lesions are tough fibrous nodules with few lymphocytes, though there may be some epithelioid cells.

Healed tubercles may be found at autopsy not only in the lungs, but in the spleen, liver, and other organs.

### LEPROSY

Leprosy, like tuberculosis and syphilis, is an infective granuloma, and a comparison of these three diseases makes a good exercise for the student of pathology. It is caused by *Bacillus lepræ*, an acid-fast bacillus closely resembling the tubercle bacillus. Unlike the tubercle bacillus, the bacillus of leprosy has not been cultured, nor have laboratory animals been infected successfully. The exact mode of infection is not known, but it is probably by direct contact. Ulcerated lesions of the nose and skin may discharge enormous numbers of bacilli. In spite of the popular opinion, the disease is only slightly contagious. Intimate and long-continued contact is necessary for infection to occur. Nurses and doctors in charge of leper colonies are very seldom infected if they take proper precautions. The incubation period is long and the exact time unknown.



FIG. 66.—Nerve lesion in leprosy. Nerve bundles bound together by fibrous tissue.  $\times 18$ .

The bacilli are distributed widely throughout the body, but the most important lesions are those of the skin and the nerves. Corresponding to these lesions two clinical types are recognized, the *nodular* or *tubercular form* and the *anesthetic form*. In the former nodules or masses are formed in the skin, particularly of the face, hands, and feet; in the latter there are anesthetic patches on the skin. The two forms are frequently combined. A cellular granulation tissue is formed. This is composed mainly of large mononuclear cells known as *lepra cells*. These usually have a pale foamy appearance owing to a high lipid content. They may be crowded with acid-fast bacilli, the source of the lipid. Some of the cells attain a large size and may be called *giant cells*, but they are quite different from the multinucleated giant cells of tuberculosis. The new granulation tissue is diffuse, and does not show the grouping of the cells into follicles so characteristic of tuberculosis. Nor is

there any caseation, but ulceration of the superficial lesions is common, so that there may be great destruction of the fingers, nose, ears, etc., with terrible disfigurement. Leprous lesions are found in the liver, spleen, and other organs.

The lesions of the nerve trunks are peculiar to leprosy. They occur in the nodular as well as in the anesthetic form. There is a perineuritis, and the thickened nerves can be felt as cords under the skin of the arm and leg. The bacilli penetrate between the nerve bundles, and there is first a formation of loose granulation tissue and later fibrosis. (Fig. 66.) The nerve fibers are destroyed, so that anesthetic areas are produced, followed later by motor and trophic disorders. The destructive lesions already mentioned may be partly trophic, but in part they are due to loss of sensation with subsequent injury.

The clinical diagnosis is seldom difficult (nodular lesions and anesthetic patches), but in doubtful cases the acid-fast bacilli can be demonstrated in the discharge from the nose and the skin lesions, or a section of skin can be removed and stained for lepra bacilli. In active cases of the cutaneous type myriads of bacilli may be found in smears of serum made from a small incision in any part of the skin, even though it may appear quite normal. In the nerve lesions, on the other hand, bacilli can seldom be detected.

### SYPHILIS

Syphilis is a spirochetal infection in which the organisms enter through the skin or a mucous membrane, and become widely distributed throughout the body long before a local lesion is produced. Every organ may be infected, and nearly every disease may be simulated by syphilis. Of all diseases it is the most subtle. It is a master of disguise. There is no symptom which it cannot cause, no syndrome for which it may not be responsible. The incidence is said to be not less than 5 per cent of the population. At least 500,000 new cases occur every year in the United States. It is more common than measles, twice as common as tuberculosis and is responsible for 10 per cent of all cases of insanity. It is therefore essential to keep syphilis in mind in every differential diagnosis. The problems of the etiology and treatment of syphilis have engaged the attention of investigators for hundreds of years, but the fundamental contributions to our present knowledge were all crowded into the first decade of the twentieth century. In 1903 Metchnikoff and Roux succeeded in inoculating a chimpanzee with syphilis, in 1905 Schaudinn and Hoffman discovered the *Spirochaeta pallida*, in 1906 Wassermann published his complement-fixation test, and in 1910 Ehrlich introduced the arsenical treatment ("606") to the medical profession. In the knowledge of no other disease have such extraordinary advances been made in so short a time. One of the most remarkable chapters in the history of syphilis is the story of how John Hunter inoculated himself on the glans and prepuce with the discharge from a venereal sore, and proceeded to observe and record with the detachment of the scientist the lesions as they appeared and disappeared over a period of three years. He experimented with various forms of mercurial treatment, but always stopped when there appeared to be danger of curing the disease. The story may be read in Long's Readings in Pathology.

***Spirochaeta Pallida*.**—The *Spirochaeta pallida* (*Treponema pallidum*), discovered by Schaudinn in 1905, is a delicate spiral-shaped organism,

actively motile, with 6 to 15 sharp spirals. It is stained only with great difficulty by aniline dyes, and can be grown only under strictest anaerobic conditions. These reasons helped to delay its discovery so long. The name "pallida" is earned by its pale appearance in stained smears. Spirochetes are present in all syphilitic lesions, but primary and secondary lesions are far more infective than tertiary lesions, for in the latter the spirochetes are very scanty. The lesions of congenital syphilis are particularly dangerous, as they are swarming with spirochetes.

The disease can be transmitted to the lower animals, most easily to the monkey and the rabbit. It is best to inoculate the virus into the external genitals of the monkey and the testicle of the rabbit.

It is probable that there are different strains of spirochetes, some of which may have a tendency to attack a special tissue such as the nervous system. It is, however, still difficult to be certain if the site at which a lesion develops depends more on tissue factors or on spirochetal factors.

The spirochetes can be demonstrated in three ways:

1. *By Dark-field Illumination.*—The spirochetes are examined living, and are recognized by their active motility and their sharp cork-screw spirals. This is the best method for primary lesions and secondary lesions which are discharging. The method is liable to grave error in lesions of the mouth, as the *Spirochæta pallida* is easily confused with the other spirochetes normally occurring there.

2. *By Stained Smears.*—The spirochetes may be faintly stained by means of Giemsa's stain or a modified Fontana (tannic acid and silver) method. When the infected material is mixed with India ink and a smear made, the background is black and the spirochetes stand out unstained.

3. *By Silver Impregnation.*—The original Levaditi method or the various modifications such as that of Warthin and Starrey are used for showing the spirochetes in the tissues. The silver impregnation method is not easy, and even in the best hands the results are variable.

**Natural History of the Disease.**—In the vast majority of cases infection is acquired during sexual intercourse. The spirochetes may be present in recent lesions on the genital organs, or they may be transmitted in the semen many years after the original infection. There may be extragenital infection on the lips (kissing), mouth, tongue, fingers, or nipple (nursing an infected child). The spirochetes may penetrate an unbroken mucous membrane, but it is unlikely that they can enter the skin unless there is some crack or abrasion.

Syphilis is a general systemic infection in the course of which certain local lesions are produced which are sufficiently striking to attract clinical attention. Long before the first lesion (chancre) appears the spirochetes have infected the entire body. When an infected needle is passed through a rabbit's testicle and the testicle removed in forty-eight hours, in a week's time the blood is so heavily infected with spirochetes that 0.5 cc will transmit the disease.

When the spirochetes penetrate the surface they invade the perivascular lymph spaces, multiply exceedingly, and pour into the



regional lymphatics and the blood stream. It is evident that no treatment of the local lesion, which only develops after general infection has occurred, can have any effect on that infection. The disease is divided clinically into three stages. These stages indicate that different sets of tissues are developing a hypersensitiveness which causes them to react to the irritant sufficiently violently to produce the symptoms of disease. The organs vary in the time they take to develop this hypersensitiveness, some are early, others late. The stages are separated by curious latent intervals. These stages and intervals have nothing to do with the spread of the infection, for that has already taken place.

Brown and Pearce have shown in the rabbit that the duration of a lesion is inversely proportional to the intensity and extent of the local reaction. The latter determine the clinical manifestations of the disease. The same is true for the disease as a whole. If the early manifestations are severe the later ones are likely to be slight. On the other hand an initial lesion so mild as to pass unnoticed may be followed years later by a disastrous involvement of the nervous system. This "law of inverse proportions" is as true for the human patient as for the experimental animal.

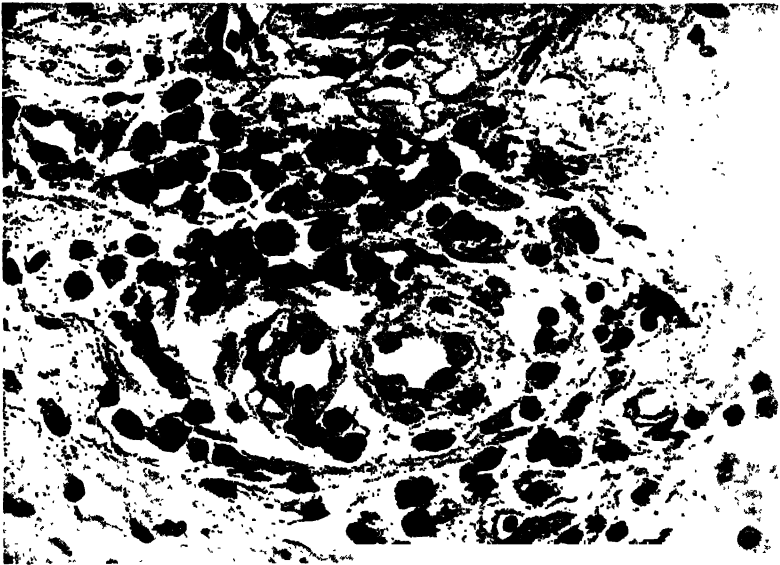


FIG. 67.—Syphilitic reaction. Lymphocytes and plasma cells collected around two small vessels with swollen endothelium.  $\times 500$ .

The spirochetes in the perivascular lymph spaces excite the syphilitic reaction. This consists of an accumulation of mononuclear cells, chiefly lymphocytes and plasma cells. (Fig. 67.) The latter is the characteristic cell of syphilis; in tuberculosis it is not at all prominent,

but in non-specific inflammations it is sometimes present in large numbers. The new tissue is highly vascular in comparison with the avascular lesion of tuberculosis. Swelling of the endothelium lining the capillaries may cause narrowing of the lumen or obstruction. Fibroblasts are stimulated to proliferate, and when healing sets in there may be marked fibrosis. In late lesions (tertiary stage) necrosis is frequent (gumma formation) and is associated with the presence of giant cells, but these are far less numerous than in tuberculosis.

It will be seen that there is nothing pathognomonic about the histological changes in syphilis. The most characteristic feature is perivascular collections of lymphocytes and plasma cells, with, in the later stages, formation of gummata. At the same time the site of the lesion (as a rule quite different from that of tuberculosis) and a knowledge of all the facts of the case will usually enable the pathologist to arrive at a correct diagnosis. In doubtful cases the tissue may be stained for spirochetes.

As the result of the inflammatory reaction the spirochetes die out locally and healing occurs with replacement of the inflammatory cells by fibrous tissue. But unfortunately clinical healing does not correspond with cure, and some of the spirochetes may survive. In the course of time the tissue immunity wears off, and then the spirochetes revive, multiply again, and cause a relapse. This sequence of events may take place in any part of the body, although it is least likely to occur in the primary lesion where the local reaction has been most violent. The testicles may appear normal clinically, but virulent spirochetes may be discharged in the semen years after the Wassermann reaction has become negative and all gross signs of the disease have disappeared. It is evident that clinical healing is not synonymous with the cure of the disease.

Warthin has shown that, particularly in the parenchymatous organs and the vascular system, there may be no sharp reaction, but merely a low-grade inflammation accompanied by degeneration and fibrosis. There is an adaptation, a partial tolerance of host to organisms or organism to host, which is particularly unfortunate because it prevents the violent reaction which alone can lead to self-cure.

**Immunity.**—Syphilis conveys a marked degree of immunity. Under ordinary circumstances a syphilitic patient cannot be infected a second time. But this is not invariable. Many cases are on record where a patient with active syphilis has been reinfected, particularly in the early stages of the disease. A rabbit can develop a second chancre up to the end of the second month, but not after the third month. The immunity appears to depend on the local reaction. If this is interfered with, so is the immunity. The immunity has nothing to do with the blood. It is a true tissue immunity. It is commonly believed that there can be no immunity without infection, that once the spirochetes are destroyed immunity is at once lost. The work of Chesney has thrown doubt on this doctrine. He has shown that in the experimental animal (rabbit) immunity may persist even though

infection has been entirely eliminated. Whether this is true of man it is almost impossible to say. It seems doubtful if man, once infected, can ever be entirely freed of the *Spirochæta pallida*.

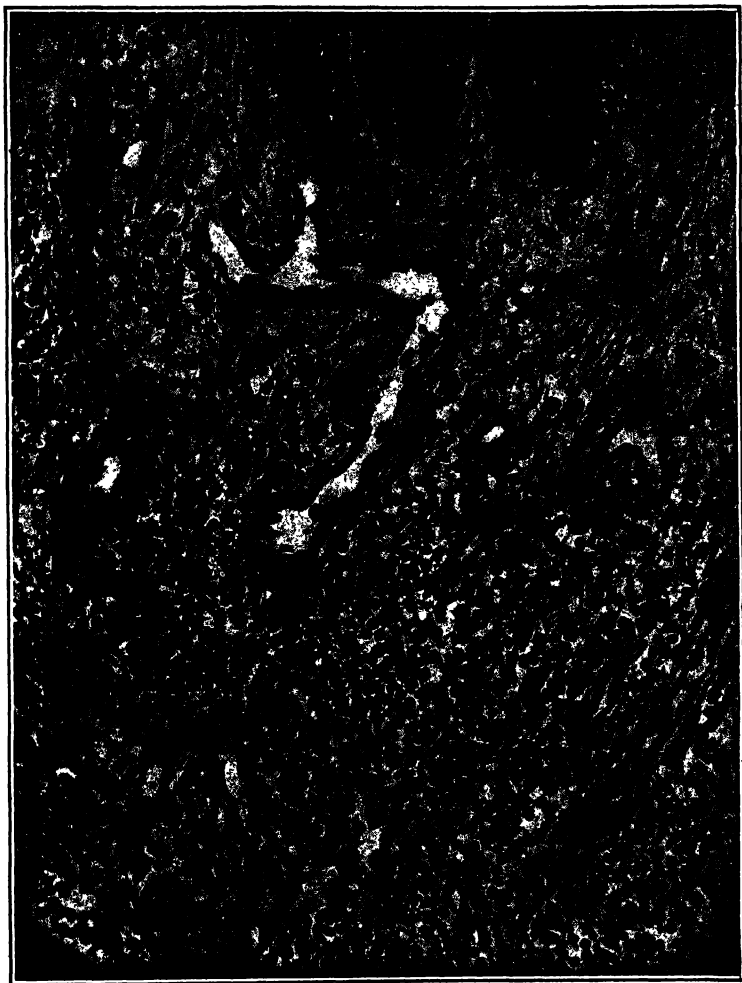


FIG. 68.—Primary syphilitic lesion showing surface epithelium, marked vascularity, swelling of vascular endothelium, and dense round-cell infiltration.  $\times 250$ .

Sex and particularly pregnancy bears some strange relation to the clinical manifestations of the disease. These are nearly always milder in women. Moreover, pregnancy and lactation markedly reduce the severity of the symptoms.

**The Primary Lesion.**—The primary lesion appears at the site of inoculation. This is usually on the genitalia, but it may be extragenital

(lip, fingers, etc.). The common genital sites are the penis in the male and the cervix in the female; the cervical chancre is highly infective on account of the moist character of its surroundings and it is easily overlooked owing to its hidden nature and freedom from pain and discharge. The primary lesion is generally single but may be multiple. It usually develops in from three to four weeks after infection, but this latent period may be as short as two or as long as six weeks. It first takes the form of a hard nodule, but the surface tends to become ulcerated and a "hard sore" or *chancre* is formed from the surface of which enormous numbers of spirochetes are discharged. These are most readily detected by means of the dark-field method. The chancre is the earliest clinical manifestation, but from the pathological standpoint the chancre is really a late affair, as we have already seen. The induration is due to dense cellular infiltration, but does not appear for the first few days. The floor of the ulcer is a dull red, but later it becomes glazed and coppery. It is characteristically insensitive. In the course of a few weeks healing occurs. Whether or not a scar is left depends on the amount of tissue destruction.

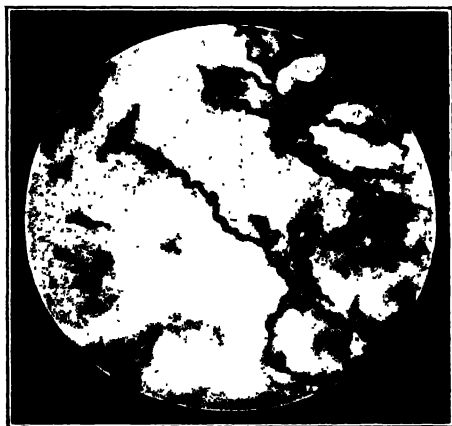


Fig. 69.—Spirochetes in tissue stained by the Levaditi method.  $\times 2500$ .

The microscopic appearance is that of all syphilitic lesions but lacking in "late" features; there is a dense accumulation of lymphocytes and plasma cells especially around the small vessels, and fibroblasts multiply and lay down collagen fibrils. (Fig. 68.) Destruction of tissue is seldom marked, but the surface epithelium is usually lost. If the section is stained by the Levaditi method an incredible number of spirochetes are brought to view. (Fig. 69.)

**Primary Lymph Node Enlargement.**—The regional lymph nodes (inguinal, submental, etc.) are enlarged in the primary stage. These nodes are hard and shotty, but not painful or tender. They thus resemble the chancre in all respects. Microscopically the nodes usually merely show a diffuse hyperplasia. Puncture of the nodes will show spirochetes in the dark-field, and sections stained by the Levaditi method contain great numbers of spirochetes.

**The Secondary Lesions.**—After the appearance of the primary lesion there is a latent period during which apparently all is well. This affords an excellent illustration of the difference between infection and clinical disease. Every tissue is infected and yet there are no signs of this. At the end of from two to three months after infection the tissues of ecto-

dermal origin develop the power to react and lesions appear in the skin, mucous membranés, and central nervous system. These persist for a period of months and then disappear. There is no destruction of tissue (necrosis) at this stage, so that no scars are left, but there may be some coppery pigmentation. After the disappearance of a secondary lesion there may be a recurrence at the same place. This is due to the local immunity being exhausted, so that a few surviving spirochetes start to multiply afresh and the whole process is repeated. In this way constant reinfections occur so that the disease never dies out.

**Lymph Nodes.**—Secondary lymphadenitis is one of the earliest changes. The nodes all over the body are enlarged in distinction to the regional involvement of the primary stage. The enlargement is never great, but it may persist for months or years. Swelling of the epitrochlear and posterior cervical nodes is specially characteristic. Microscopically there is usually only diffuse hyperplasia, but the nodes may show tubercles composed of epithelioid cells and giant cells exactly like those of tuberculosis; these may be regarded as miliary gummata, but necrosis which is so characteristic of the gumma is not seen at this stage.

**Skin.**—The lesions of the skin are of great variety, but they are symmetrical in distribution (tertiary lesions are asymmetrical), they are polymorphous in type, *i. e.*, present several varieties of lesion at the same time, they possess a copper tinge, and their outline is that of the segment of a circle. Like other secondary lesions they do not destroy tissue. If the cellular accumulation is slight and vascular dilatation marked the lesions are *macular* like the rash of measles. If the cells are more abundant the lesions become *papular*. Infection may make these *pustular*. A more advanced stage with necrotic patches and crust formation is called *rupia*. A *condyloma* is a large flat papule occurring in moist situations, *i. e.*, between the vulva, around the anus, etc. These are swarming with spirochetes and are highly infectious. A scaly condition of the palms of the hands and the soles of the feet is a late manifestation.

The appendages of the skin may also suffer. The hair comes out, and the nails become brittle and fissured, a condition of *syphilitic onychia*.

**Mucous Membranes.**—Sore throat is one of the commonest symptoms. There may be *mucous patches* of the mouth, pharynx, and vagina. These are flat superficial lesions which have been appropriately likened to the track left by a snail. They swarm with spirochetes and are highly infectious.

**Central Nervous System.**—There may be neuralgic symptoms and paralysis of the eye muscles, but, although the nervous system is infected at a very early date, serious symptoms seldom appear before the tertiary stage. The cerebrospinal fluid shows increase of lymphocytes and of globulin, but spirochetes can be demonstrated by animal inoculation before there are any changes in the fluid.

**Eye.**—Iritis is common.

**Bones and Joints.**—Periostitis causes a painful and tender swelling more particularly of the tibia, clavicle, sternum, and cranium. The pain is nocturnal, being aggravated by the increased vascularity caused by the warmth of the bed clothes. One or more joints may show a mild inflammation.

**The Tertiary Lesions.**—The subsidence of the secondary lesions is followed by another latent interval during which all is quiet. In a year or not for many years a third set of lesions appear. These are not symmetrical, they affect deep as well as superficial structures, and they show a tendency to necrosis and destruction. They are only slightly infective, for they contain only a few spirochetes. These are not easy to demonstrate in silver preparations.

Two main types of tertiary lesion may occur. The one is gross and localized (the gumma), the other is microscopic and diffuse. The gumma is readily recognized, but is much less common than the diffuse syphilitic inflammation.

**The Gumma.**—This is a necrotic localized syphilitic lesion composed of the usual mononuclear inflammatory cells. The vessels show periarteritis and endarteritis. In the center of the lesion necrosis and caseation occur with the formation of a peculiar gummy material. At the margin of the caseous center giant cells may be seen, but these are not so numerous as in tuberculosis. There is not the same complete loss of structure as in tuberculous caseation. Fibroblasts proliferate and may form a fibrous wall around the lesion. A tuberculous lesion usually shows tubercles in the surrounding tissue, but the syphilitic gumma is solitary and unattended. The characteristic degeneration is usually attributed to the action of the spirochetes and the vascular changes, but vascular changes are present in the primary and secondary lesions, and spirochetes are infinitely more numerous. It seems more likely that the change is in the nature of an allergic phenomenon due to an alteration in the reactivity of the tissues. In the *gross* a gumma is a yellowish homogenous mass of rubbery consistence which may be as small as a pea or as large as an orange. Ulceration of the overlying tissue (skin, mucous membrane) is common.

In the *skin* a gumma forms a hard painless lump in the subcutaneous tissue. The overlying skin may be ulcerated. The tertiary syphilitic ulcer is punched-out, with wash-leather base and serpiginous outline owing to healing at one place with breaking-down at another. The resulting scar is often pigmented. Scars around the knee and in the upper third of the leg should suggest syphilis.

In the *mouth* tertiary lesions are common. The *pharynx* may be ulcerated. Perforation of the *soft palate* suggests syphilis. The *tongue* shows either ulcers or a diffuse thickening which will be described in connection with that organ. Syphilis of the tongue is a precancerous lesion when the surface is involved. The *larynx* may be ulcerated and the vocal cords destroyed, causing a characteristic hoarseness of the voice. Gummatus destruction of the *nose* may produce an equally characteristic saddle-shaped depression of the bridge.

Gummata are not common nowadays in the viscera. The *liver* may show one or many masses (Fig. 70), which heal with fibrosis so that deep scars are formed. These produce a peculiar lobed appearance known as *hepar lobatum*. In the *testicle* the gumma forms a hard mass with characteristic loss of testicular sensation on palpation. It may break down and ulcerate through the skin. There may be *gummata* in the bones, chiefly the tibia and cranium. In the *brain* a gumma usually grows from the meninges and presses on the brain; it is likely to be mistaken for a tumor.

**Diffuse Lesions.** — The spirochetes are widely distributed, and may set up a diffuse chronic inflammatory reaction in the perivascular lymph spaces. There are the usual accumulations of lymphocytes and plasma cells, often around the small vessels. There is no caseation, but as a result of the long-continued irritation there is a gradual degeneration of the parenchymatous structures and their replacement by fibrous tissue. Syphilis of the aorta and of the vascular system generally is of this diffuse type. In the testicle and other internal organs the diffuse lesion is much commoner than the gumma. The most serious of all the lesions are those of the central nervous system which may come on many years after the initial infection. These may affect chiefly the meninges (syphilitic meningitis), the brain (general paresis of the insane), and the spinal cord (tabes dorsalis).



FIG. 70.—Gumma of liver.

**Congenital Syphilis.**—Syphilis may be transmitted from the father or the mother, but in all cases the mother is infected, although often she shows no evidence of the disease. The beneficial effect which pregnancy has on the disease has already been mentioned. There are three possibilities. (1) The child may be born dead, usually showing well-marked evidence of syphilis. Syphilis is an important cause of still-birth. (2) The child may be born alive with external evidence of syphilis. (3) The child may appear healthy, but lesions develop later.

When the child is born dead the appearance is usually characteristic. There is no primary lesion, as infection takes place through the placenta. The child is usually premature and undersized. The skin may be macerated. If not, it usually shows bullæ. The spleen is enlarged, and often the liver. Syphilitic epiphysitis is one of the commonest and most diagnostic features. It is best seen at the knee by splitting open the lower end of the femur or upper end of the tibia. In place

of the normal thin, regular, white epiphyseal line there is a broad irregular somewhat yellow line which is highly characteristic.

The chief *microscopic* change at this stage is an interstitial round-cell infiltration of many of the internal organs combined with a varying degree of fibrosis. In the liver this produces a fine form of intercellular cirrhosis. Levaditi preparations of the liver, heart, adrenals, etc., show enormous numbers of spirochetes. It is evident how infectious such a body must be, and great care is necessary in performing an autopsy.

If the child is born alive the skin may show the varied lesions already described in the acquired form. Common sites for the lesions are the buttocks, anus, angles of the mouth, and the palms of the hands and soles of the feet. Radiating scars are formed at the angles of the mouth which are very characteristic. The skin is often wrinkled, so that the child has a dried-up, wizened appearance. Enlargement of the spleen is very constant. The liver and other organs show the changes already described. The mucous membranes show the same lesions as in the acquired form. In the nose there is ulceration and destruction, so that the bridge of the nose may fall in giving the characteristic "saddle nose" of congenital syphilis. One of the most useful aids to diagnosis is roentgenographic evidence of epiphysitis and periostitis in the long bones.

In the late type lesions develop over a period of years which stamp the patient as being a congenital syphilitic. The permanent teeth show the appearance known as "Hutchinson's teeth;" these are small, widely-spaced, peg-shaped (narrow at the apex), and the central incisors are notched. The molars are pitted and honey-combed. An interstitial keratitis develops at the time of puberty producing a ground-glass opacity in the cornea. Nerve deafness is common. The scars at the angles of the mouth known as rhagades have already been mentioned. Gummata develop in the bones, or a diffuse thickening affecting especially the tibia ("saber tibia"). There may be involvement of the central nervous system similar to that seen in the acquired form (juvenile paresis and juvenile tabes).

**Bejel.**—This remarkable condition appears to be a non-venereal form of syphilis which is prevalent amongst the Bedouin Arabs. About 75 per cent of the Bedouins show evidence of infection, although there is no gonorrhea amongst them, and sexual promiscuity is unknown. It is a disease of the whole community, like measles, and is acquired in childhood, the infection being contracted from some other child in the acute stage, probably by means of drinking vessels. The earliest lesions are gray patches about the mouth, followed by a papular eruption on moist areas. In about a year, the lesions vanish, and the child appears healthy. They may never recur, but frequently gummata of bones, skin and pharynx appear many years later. The cardiovascular and nervous systems are not attacked. The Wassermann and Kahn reactions are positive.

**Lymphogranuloma Venereum.**—This venereal disease is commonly known as lymphogranuloma inguinale, but as that name is continually confused with granuloma inguinale, lymphogranuloma venereum is to be preferred. Climatic bubo is another name by which the condition is known. The best and least



confusing term is lymphopathia venereum, first suggested by Wise and Sulzberger in 1932, and distinguishing the condition sharply from granuloma inguinale. It is a contagious venereal disease caused by a filterable virus, which can be transferred to the monkey, rabbit and guinea-pig. The infection may, however, be non-venereal in children, doctors, nurses, and research workers. The virus is present in the primary lesion, regional lymph nodes, urethral and vaginal discharges, pelvic abscesses, blood stream, and spinal fluid. It has been demonstrated forty years after the original infection. The initial lesion is on the glans or vulva; it is small and indurated, heals quickly, and may never be noticed. Several weeks later the inguinal nodes become enlarged, indurated, matted together and painful, the overlying skin assumes a bluish-red color, fluctuation develops, and a purulent fluid is discharged, leaving a chronic ulcer of the skin with sinuses; these lesions may be extremely slow in healing. The microscopic picture is that of a chronic granuloma, not in any way specific, consisting largely of epithelioid cells with necrosis, and thus resembling tuberculosis, but caseation never occurs. When sterilized purulent fluid from one of the nodes is injected intracutaneously in a person suffering from the disease, it produces a marked allergic skin reaction. This is known as the intradermal test of Frei and Hoffmann, and the skin allergy on which it depends persists throughout life. When the virus is injected into the brain of monkeys or mice a meningo-encephalitis is produced, and brain emulsion makes a stable antigen for the Frei reaction which is preferable to using material from an infected person. Marked increase in the plasma protein is common. The disease is commoner in the negro but it often occurs in the white. Cole saw 52 cases in one year in Cleveland. Rectal stricture is a common complication, and in the past has been incorrectly attributed to syphilis. Most authors agree that rectal lesions are much commoner in women, but Mathewson reports 74 cases in San Francisco, of whom 60 were men and only 14 women. The site of the primary lesion and not the sex determines the incidence of secondary lesions in the inguinal nodes or the rectal nodes. Owing to lymph drainage, infection of the glans and prepuce in the male and the clitoris and vulva of the female lead to inguinal lesions, whereas infection of the posterior urethra in the male and the vagina in the female are responsible for inflammatory lesions and subsequent stricture of the rectum. On these grounds rectal lesions might be expected to be more frequent in the female. The Frei-Hoffmann test is particularly useful in these cases of rectal stricture in the female with no external evidence of the disease. Lymphogranuloma venereum must not be confused with granuloma inguinale (see below). In the former the essential lesions are in the lymph nodes with secondary involvement of the skin, while the latter is primarily a disease of the skin. The presence of the Frei-Hoffmann test and the absence of Donovan bodies serve to characterize lymphogranuloma venereum.

### GRANULOMA INGUINALE

This is a chronic infective granulomatous condition practically confined to the negro and of common occurrence in the tropics and the southern part of the United States. It occurs in the anal and genital regions, commonly commencing on the penis and labia. The microscopic features are granulation tissue with a massive cellular infiltration, mainly plasma cells and remarkably few lymphocytes, together with a peculiar cell which Pund and Greenblatt have shown to be specific for this condition. The pathognomonic cell is a large mononuclear cell from 25 to 90 microns in diameter, presenting many sharply defined intracytoplasmic spaces which contain small deeply-staining round or rod-like bodies. The mode of transmission is not certain. Puncture of the granulomatous lesions shows the presence of numerous intracellular rod-like bodies in the mononuclear cells. These were first described by Donovan, and are best called Donovan bodies (to be distinguished from Leishman-Donovan bodies of kala-azar). The organism can now be cultivated

on the yolk-sac of the developing chick embryo, and it has been named *Donovania granulomatis*. Occasionally the lesions are found in other parts of the body—face, mouth, back. It runs a chronic course, but responds in a remarkable manner to intravenous treatment with tartar emetic.

### THE MYCOSES

The mycoses are diseases produced by the higher fungi. The lesions are granulomatous in nature, and may therefore be ranked with those of tuberculosis, syphilis, and leprosy, but suppuration is common.

**Actinomycosis.**—This is the commonest of the mycoses in man, but the disease is much commoner in domestic animals (horses, cattle, pigs). It is caused by *Actinomyces bovis* or ray fungus, so-called because of the radiate arrangement of threads at the edge of the colonies. The fungus is a streptothrix which forms little yellow clumps in the tissue known as "sulphur granules." These clumps are composed of a felted mass of filaments with spores and club-shaped bodies at the periphery. The filaments are Gram-positive and the clubs Gram-negative. There are several types of actinomyces, some aerobic, others anaerobic. The great majority of human and animal infections are due to anaerobes.

The method of infection is still uncertain. There is no evidence that it is conveyed directly from animals to man, but it is much commoner in farmers and other country-dwellers. Ears of grain have been found embedded in the mouth lesions, and the usual view is that infection is carried by grain which has been chewed, but the *Actinomyces bovis* has never been found in grains or grasses in a state of Nature. The fungus probably becomes an inhabitant of the mouth or intestine in country-dwellers, and enters the tissues through some break in the surface, the root of a carious tooth, etc. Secondary invasion by pyogenic organisms is common, and the resulting suppuration may reduce the oxygen tension in the tissues and favor even more the growth of anaerobic actinomyces. When once penetration of the surface has occurred the wound heals promptly, and the pathological process works away from the mouth, intestine or rectum as the case may be.

A much rarer form of actinomycosis is that caused by *Nocardia asteroides*, which is aerobic in contrast to the anaerobic *Actinomycosis bovis*. The lesions are far more widespread, involving a large number of organs as well as lymph nodes.

**Spread.**—The spread is different from that of tuberculosis and syphilis, for the lymph vessels and nodes are not involved, a valuable point in diagnosis. The infection starts in the subcutaneous or sub-mucous tissue and spreads by direct continuity. The lesion may rupture into a bloodvessel, and there may be blood spread to the liver, brain, and heart, but this is not common.

**Lesions.**—The lesions occur in four chief sites: (1) head and neck (60 per cent), (2) ileocecal region and appendix (20 per cent), (3) lungs (15 per cent), and (4) the skin (5 per cent). A firm mass develops,

usually under the lower jaw, followed by a brawny induration of the neck. After a time the mass breaks down and becomes riddled with abscesses and sinuses. These multiple sinuses perforating the skin are characteristic of actinomycosis. There is progressive destruction of connective tissue, muscle, and bone. The pus contains the tiny yellow *sulphur granules* from which the diagnosis can most readily be made. (Fig. 71.) These should be looked for whenever the abscess is opened, as they may disappear later. In the *abdominal form* a firm mass is formed in the cecum or appendix, which is very apt to be mistaken for carcinoma. Suppuration occurs and sinuses are formed in the abdominal wall. I have seen perianal lesions, probably from infection through the skin. In the *lungs* multiple abscesses are formed; these are surrounded by fibrous tissue, and the condition is easily mistaken for tuberculosis.

*Microscopic Appearance.*—The microscopic appearance is that of a granuloma with the addition of suppuration. (Fig. 73.) There are chronic inflammatory

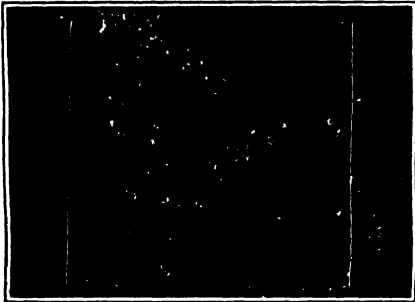


FIG. 71.—Sulphur granules, photographed on slide with black background.



FIG. 72.— Colony of fungus in actinomycosis. Many mycelial threads can be seen in addition to the dense felt-work at the periphery.  $\times 275$

cells, fibroblasts, and giant cells. If suppuration is marked the picture approaches that of acute inflammation. It is uncommon to find colonies of the fungus (Fig. 72); these are much more easily demonstrated in the discharge. It is evident that the histological appearance is not at all characteristic, and that not much need be expected from biopsy examination.

**Actinobacillosis.**—This is an epidemic disease in cattle, very rarely affecting man. It closely resembles actinomycosis, but with the important difference that the lymph nodes are constantly involved. The pus is very viscous, and contains greyish-white granules. The center of the granules consists of a mass of minute Gram-negative bacilli, known as the actinobacillus, surrounded by radially disposed clubs. Thus the center of the granule is Gram-negative, whereas in actinomycosis it is Gram-positive.

**Blastomycosis.**—This is a chronic granuloma caused by a yeast-like fungus known as blastomyces. The organisms are spherical, two or three times the diameter of a red blood corpuscle, and show two characteristic features: (1) a clear double contour, and (2) budding-like yeast cells. They are demonstrated in the discharge from the lesions by adding a few drops of sodium hydroxide to the pus and examining unstained. The method of infection is unknown, but presumably it is through the skin by contagion. The disease occurs in two forms, cutaneous and systemic.

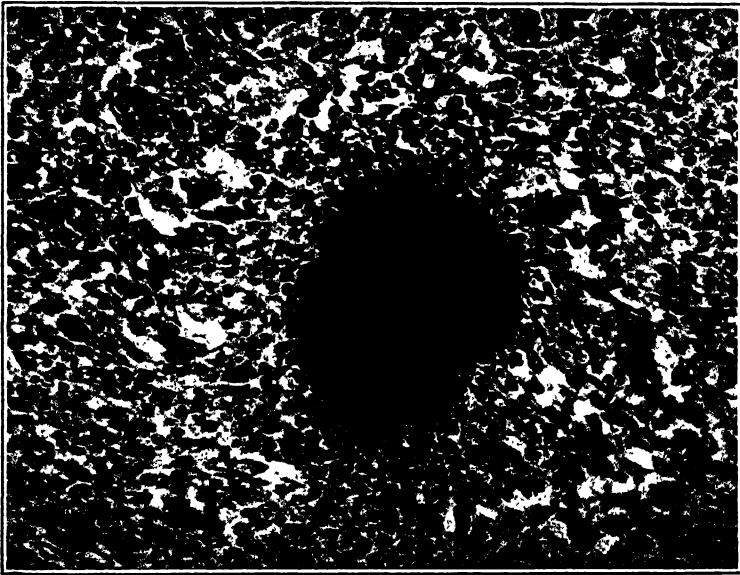


FIG. 73.—Actinomycosis showing suppuration immediately around central mass of ray fungus, and granulomatous lesion farther out.  $\times 200$ .

**Cutaneous Form.**—The cutaneous form is known as blastomycetic dermatitis. The lesions are commonest on the face, the back of the hand, and the front of the leg. At first they are papules, but they undergo suppuration and ulcerate. The disease spreads over the surface, so that a large area may be involved. The microscopic picture is similar to that of actinomycosis, *i. e.*, a granuloma (lymphocytes, mononuclears, giant cells) with suppuration added. At the edge of the ulcer there may be very marked epithelial hyperplasia which may closely simulate the appearance of epidermoid carcinoma. The spherical fungi are seen in sections of the tissue or in smears of the discharge.

**Systemic Form.**—The systemic form is much less common. The lungs are most often involved, but any organ may be affected. Infection is spread by the blood stream. The pulmonary lesions are nodules in abscesses and are very liable to be mistaken for tuberculosis. The fungi are very numerous in the tissues in the systemic form. This

form is nearly always fatal, but the cutaneous form is seldom fatal and may last for many years. The various lesions are well illustrated in Baker's paper.

**Sporotrichosis.**—This is a chronic infection caused by the fungus *Sporotrichum*. In many respects it closely resembles blastomycosis, but the fungus is demonstrated by culture, not in smears. Like blastomycosis it is usually confined to the skin, but occasionally the internal organs are involved. The skin lesions are, as a rule, on the hand or forearm. They take the form of nodules which later break down and suppurate. The infection advances along the lymphatics, so that a line of nodules is formed along the arm, an appearance always suggestive of sporotrichosis. The microscopic picture is the same as in actinomycosis and blastomycosis, i. e., a granuloma with suppuration. The disease is very chronic but is rarely fatal.

**Coccidioidomycosis.**—This uncommon disease was originally thought to be confined to the San Joaquin valley, California, so that it came to be known as the "California disease." It is now known to be distributed all over the United States. It is an infective granuloma closely resembling tuberculosis, but caused by *Coccidioides immitis*, a yeast-like fungus. This is a spherical body with a double-contoured highly refractile capsule. It resembles the blastomyces, but can be differentiated by the fact that it multiplies by the formation of endospores, the blastomyces by budding. The coccidioides are much larger and may measure 50 microns. (Fig. 74.) Clinically the disease is easily mistaken for tuberculosis, syphilis and blastomycosis, and many cases of supposed tuberculosis are probably examples of this disease. Infection is due to the inhalation of dust containing the fungus. There is no passage of the infection from man to man. The morbidity is high, but the mortality relatively low. The infection has also been found in cattle. The disease can be reproduced in the guinea-pig, the characteristic lesion being a suppurative orchitis.



FIG. 74.—*Coccidioides* in tissues.

The lesions are usually in the lungs, bones and skin, but any organ may be involved. They are in the form of granulomatous masses and abscesses. They cannot be distinguished from those of tuberculosis with the naked eye, but it may be said that in the lungs there is less cavitation than is usual with tuberculosis and in the bones the lesions are more extensive. The microscopic appearance also resembles that of tuberculosis; tubercle formation, epithelioid cells and giant cells are common. (Fig. 75.) The pathognomonic feature is the presence of the double-contoured highly refractile coccidioides filled with spores. These are also found in pus from the lesions. The diagnosis is confirmed by inoculation of a male guinea-pig, with the development of a suppurative orchitis.

The work of Dickson has shed new light on the disease. He has shown that the condition begins as a mild infection of the respiratory tract often accompanied by erythema nodosum. The great majority recover promptly in the

course of a few weeks, but in a few cases the mild attack is followed by the chronic granulomatous disease known as coccidioidal granuloma. Dickson suggests the term coccidioidomycosis to cover both forms.

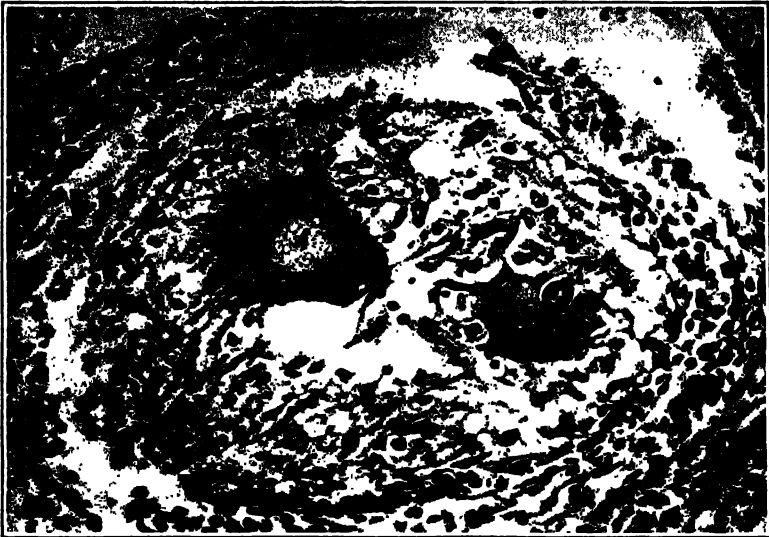


FIG. 75.—Coccidioidal granuloma. Tubercle-like lesion, the right hand giant cell containing coccidioides.  $\times 200$ .



FIG. 76.—Mikulicz cell in rhinoscleroma.  $\times 1000$ .

**Rhinoscleroma.**— This is a disease of eastern Europe, and is seldom seen elsewhere except in emigrants from that part of the world. Although not a fungous disease, it is an infective granuloma. There is a hard swelling of the nose (*rhin*, nose; *sclera*, hard) which may spread to the pharynx and larynx. The microscopic diagnosis is made from the presence of peculiar large, round, clear cells filled with a gelatinous material which may give the cytoplasm a foamy or reticulated appearance, and displace the nucleus to one side. These are known as Mikulicz cells. (Fig. 76.) They are often filled with bacilli resembling Friedländer's pneumobacillus. This bacillus is called *Bacillus rhinoscleromatis*, but it is not certain that the disease is caused by this organism.

**Rhinosporidiosis.**— This is a local inflammatory condition of the anterior nares, fairly common in India but extremely rare elsewhere, the only cases reported coming from the Argentine and the United States. It is rare in the female. The lesion takes the form of a polypoid growth in the nose composed of granulation tissue and presenting an extraordinary and characteristic microscopic picture, for the tissue is crowded with the huge parasitic cysts, each a single or-

ganism, which constitute the etiological agent. This is a fungus known as *Rhinosporidium seeberi* (first described by Seeber), which commences its life cycle as a parasite measuring 8 microns, but grows by nuclear division until it reaches a size of 200 to 300 microns and contains over 4000 nuclei which form 16,000 spores. The mature parasite, now called a sporangium, presents a double-contoured chitinous envelope with a germinal pore, through which the spores are discharged. The mode of infection and transmission is unknown.

**Glanders.**—Glanders is one of the infective granulomata, and in its chronic form may readily be mistaken for tuberculosis, syphilis, or actinomycosis. It is one of the diseases transmitted from animals to man. As it affects horses, the human disease is seen in grooms, veterinary surgeons, etc.

The disease is caused by *Bacillus mallei*, a slender Gram-negative rod resembling the tubercle bacillus. The Straus reaction is used for diagnosis. The suspected material is injected in the peritoneal cavity of a male guinea-pig, and within twenty-four hours an acute inflammation develops in the tunica vaginalis. The fluid from the tunica is implanted on potato, and a yellow honey-like culture is obtained.

Infection occurs from the nasal discharge of a diseased horse, and enters the body through a crack in the skin or the mucous membrane of the nose. After an incubation period varying from a few days to two or three weeks the primary lesion appears. At first this is a papule, later becoming a pustule. The lesions are spreading and destructive, with the formation of large irregular ulcers. The infection spreads along the lymphatics causing nodular swellings, which in the horse are known as *farcy buds*. The lymph nodes are swollen, and there is destruction of connective tissue and muscle. The *microscopic* appearance is that of an infective granuloma but without caseation. Giant cells are rare. Unless the bacilli can be demonstrated, a correct diagnosis may be extremely difficult. The infection may last for months or years; in the end it usually proves fatal.

An *acute* form occurs both in man and the horse. It is a septicemic condition, with the formation of pyemic abscesses in the lungs, liver, kidneys, etc. This condition is always fatal.

## ANTHRAX

Anthrax is also one of the diseases transmitted from animals to man. It is very prevalent in European animals, especially cattle and sheep, but is much less common in North America so that human infection is comparatively rare in this country. Infection is nearly always conveyed through the skin, rarely by inhaling infected material (wood-sorter's disease) or by swallowing it. The latter is the common method by which animals are infected, so that in them the lesions are usually intestinal. In man the lesions are nearly always in the skin; pulmonary and intestinal lesions are very rare. Infection is conveyed from the wool and hides of diseased animals, so that butchers, tanners, wool-sorters, etc., are the chief sufferers. The bristles of a new shaving brush may carry the infection. It is said that biting flies may convey infection from animals to man, but this seems open to doubt.

The anthrax bacillus is a large, square-ended, Gram-positive bacillus, the most important characteristic of which is the power of forming very resistant spores outside the body. For this reason infected wool, hides, shaving brushes, etc., may remain a source of danger for years. As the spores are not formed inside the body it is of the greatest importance when disposing of the body of an animal which has died of the

disease that no blood should be shed, otherwise the spores will remain in the ground for years and serve to infect other animals.

The *skin lesion* is the *malignant pustule*. It commences as a pimple on an exposed part of the skin (face, hands). This soon develops into a vesicle (not a pustule) containing clear serous or blood-stained fluid swarming with anthrax bacilli. The diagnosis is readily made by staining a smear of this fluid. When the vesicle bursts a black eschar is formed, around which a fresh row of vesicles develops; further out there is a brawny induration. The microscopic picture is one of acute inflammation. The rare *pulmonary* and *intestinal lesions* are similar in nature, *i. e.*, they show an acute hemorrhagic inflammation.

At any stage the bacilli may enter the blood stream causing an anthrax septicemia with infection of all the organs. This is constantly seen in highly susceptible animals such as the mouse and guinea-pig. The mortality from the skin lesions is not great, especially when the specific antiserum is used, but anthrax septicemia is invariably fatal. The postmortem findings are those of a hemorrhagic septicemia, with enlargement of the spleen, etc. From what has already been said, it will be obvious that extreme care must be taken at the autopsy to prevent the formation of spores.

### ANAEROBIC GAS-FORMING INFECTIONS

Infection of a wound by a member of the group of anaerobic gas-forming bacilli results in gas gangrene. There are three members of this group: (1) *Bacillus welchii* or *Bacillus aerogenes capsulatus*; (2) *Vibrio septique*, probably identical with the bacillus of malignant edema; (3) *Bacillus oedematiens*. These are all saccharolytic, not attacking proteins if carbohydrates are available, and they grow best in tissues containing an abundance of carbohydrate, *i. e.*, muscle and liver. To these three may be added *Bacillus sporogenes*, which has strong proteolytic powers and soon produces putrefaction with its characteristic smell. It is not pathogenic nor gas-producing, but it breaks up the proteins. *Bacillus welchii* is the commonest invader and the chief gas producer. As well as producing gas gangrene it is the cause of postmortem gas formation. Except when grown in special media it does



FIG. 77.—*Bacillus welchii*, showing capsules.  $\times 1000$ .

not form spores, but in tissue fluids it has a well-marked capsule. (Fig. 77.) The other organisms readily form spores.

These bacteria are putrefactive. They are unable to gain a footing



in living tissue until it has been devitalized. They are ordinarily saprophytes. Thus *B. welchii* was found in 80 per cent of wounds in the first World War, yet less than 10 per cent of these developed gas gangrene. Trauma and other organisms fail to activate it, but soil and dead muscle act as a spark which lights the fire. As the organisms feed on muscle sugar, it follows that early excision of dead muscle is the best prophylactic. Gas gangrene is a disease of muscle, which is at first a dull red and then becomes green or black. Bubbles of foul-smelling gas and blood-stained fluid can be pressed up and down the length of the muscle. The bacilli spread up and down the muscle in the interstitial tissue, and the muscle fibers are separated from their sheaths by toxic fluid, as a result of which they are killed and are then invaded by the putrefactive bacteria. (Fig. 78.)

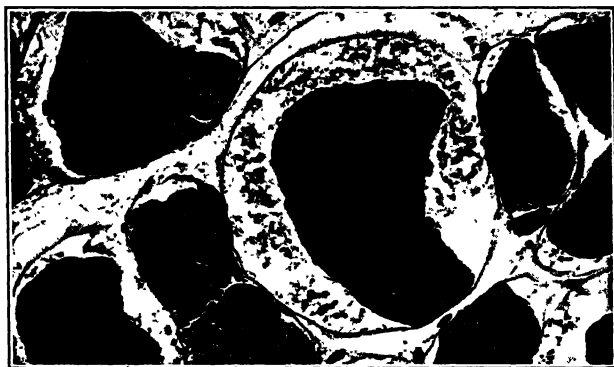


FIG. 78.—Gas gangrene. A muscle fiber separated from its sheath and from its blood supply by gas and fluid.  $\times 250$ .

The toxin of *Bacillus welchii* contains a powerful hemolysin and a substance producing necrosis of muscle, a myotoxin. Injection of animals with the hemolysin produces a blood picture similar to that of pernicious anemia. It has been thought that some of the symptoms of acute intestinal obstruction are due to absorption of *Bacillus welchii* toxin from the bowel, as it is a normal inhabitant of the bowel, and on this basis an antitoxic serum has been given in intestinal obstruction and in paralytic ileus due to acute peritonitis.

## TETANUS

Tetanus is a disease caused by wound infection with an anaerobic bacillus, *Bacillus tetani*, but it differs entirely from the group of anaerobic infections just described, for there are no local symptoms. The bacillus develops a terminal spore, which gives it the familiar drumstick appearance. The organisms can be seen in the pus from infected wounds. The disease is an infection of septic wounds, not merely a wound infection. Its growth is favored by the presence of aerobic bacteria, so that it is never found in pure culture in a wound.

The bacillus is a normal inhabitant of the intestine of the horse and other animals, and is therefore found in ground which has been manured. Wounds contaminated with garden soil, the dirt of streets, etc., are therefore always liable to infection by tetanus. This danger was so great during the World War that every wounded man received a prophylactic injection of antitetanic serum.

The *incubation period* varies greatly, averaging from ten days to a fortnight. In the case of face wounds it may be only three or four days. If the spores are surrounded by scar tissue they may remain quiescent for months. A subsequent operation, as for removal of a foreign body, may activate the spores, so that a second injection of serum should be given before such an operation.

**Absorption of the Toxin.**—The bacilli remain in the wound and produce a toxin which acts on the central nervous system. The tetanus toxin is one of the most powerful toxins known. For long it has been believed that the toxin was absorbed from the motor nerve endings and passed along the axis cylinders to reach the spinal cord. In 1934 Abel attacked this view and brought forward experimental evidence suggesting that the toxin is absorbed by the lymphatics and distributed to the central nervous system by the blood stream, where it acts on the motor nerve cells. Abel also suggested that the toxin may act directly on striated muscle, thus explaining the phenomenon of "local tetanus," which may develop in the wounded part long before the general symptoms manifest themselves. Abel's theory is supported by the observation of Barnes and Trueta in 1941, that tetanus toxin is not absorbed from an immobilized limb in an experimental animal, for lymph flow from a part ceases when it is immobilized. When the toxin reaches the cord and brain-stem it becomes so firmly anchored to the motor nerve cells that it cannot be dislodged.

The symptoms are the result of an extreme hypersensitiveness of the motor nervous system produced by the action of the toxin on the motor nerve cells. As the result of this the most trivial sensory stimuli produce a series of terrible clonic and tonic spasms, and the patient dies exhausted by his convulsions or asphyxiated by tonic spasm of the respiratory muscles. As the condition is purely toxic and not inflammatory, no characteristic lesions are found at autopsy.

*Postoperative tetanus* is fortunately rare. It is usually due to catgut infected with the spores of tetanus. When the catgut is absorbed in the wound the spores are set free and develop into bacilli. Not every case is due to the catgut. The dressings, dusting powder, etc., may be infected. Finally it must be remembered that the patient may be an intestinal carrier of tetanus bacilli which may reach the tissues through an operation wound involving the bowel.

### BUBONIC PLAGUE

The disease is caused by *Bacillus pestis*, an extremely virulent organism. It gains entrance to the body through the skin, sometimes

through the lungs by inhalation of infected droplets of sputum especially in the pneumonic form. It penetrates the skin usually by the bite of a flea which conveys the infection from the rat to man, but it may enter through cuts and abrasions. The disease may occur in endemic or epidemic forms. A human epidemic is accompanied or preceded by a rat epidemic. When a rat dies the infected fleas leave it and go in search of a new victim. The problem of plague control is the problem of the deadly triangle of the rat, the flea, and the man.

**Lesion.**—The lesions are glandular and general. The inguinal and axillary lymph nodes become much enlarged, suppurate, and form buboes. This is a regional lymph node infection, the result of inoculation through the skin. The nodes at first show ordinary inflammatory hyperplasia, but abscess formation and hemorrhage follow. The bacilli invade the blood stream and are found in enormous numbers in the internal organs, where they produce necrosis, abscesses, and toxic changes. The patient dies of an overwhelming septicemia before there is time for very marked lesions to develop.

**Pneumonic Form.**—In bubonic plague some changes are always found in the lung such as small patches of consolidation and great engorgement with large numbers of bacilli in the alveoli. Sometimes the epidemic takes a pneumonic form, in which infection is spread by tiny droplets of sputum. There are no buboes, and the patient is overwhelmed by one of the most deadly and rapidly fatal of all infections. There is not time for any extensive pneumonic consolidation, so that here also the changes are a patchy consolidation with intense congestion and alveoli crowded with plague bacilli. The rest of the body shows evidence of an overwhelming septicemia.

**Hemorrhagic Septicemia.**—This is a group of infections rather than a single disease, caused by organisms closely related to the plague bacillus (*Pasteurella* group) and affecting many of the lower animals. Members of the hemorrhagic septicemia group are chicken cholera (*Bacillus avisepticus*), swine plague (*Bacillus suisepicus*), and mouse typhus (*Bacillus typhi murium*). Some of these hemorrhagic septicemia infections may occasionally involve man. It will be realized that plague itself is a hemorrhagic septicemia.

**Whooping Cough.**—Whooping cough or pertussis is an acute infectious disease of the respiratory tract, as a result of which there are spasmodic attacks of coughing with a prolonged inspiration known as a "whoop." The disease consists of a catarrhal stage of one or two weeks' duration marked by a hard dry cough (this is the infectious period), and a paroxysmal stage of four to eight weeks' duration marked by severe paroxysms of coughing and whooping, and by attacks of vomiting. Common complications are bronchopneumonia, atelectasis, emphysema and convulsions. One attack of the disease confers immunity for life.

The *etiological agent* appears to be *Bacillus pertussis* of Bordet and Gengou, a minute Gram-negative hemophilic bacillus, which is found in great masses entangled in the cilia of the bronchial mucosa. Rich and his associates have shown that in chimpanzees the oral inoculation

of pure cultures of Bordet-Gengou bacilli resulted in a condition similar in all respects to whooping cough, and characterized by coryza followed by a protracted paroxysmal cough, associated with lymphocytosis and a positive complement fixation toward the Bordet-Gengou bacillus. On the other hand it must be admitted that whooping cough resembles a virus disease in respect to its high infectivity, the prolonged immunity which follows an attack, and the comparatively disappointing results of inoculation with vaccines of the bacilli. Rich feels that the possibility of a virus acting in conjunction with the bacilli, as is known to be the case in hog cholera, dog distemper, and influenza, cannot be dismissed.

The lesions are tracheitis, bronchitis, and the characteristic interstitial bronchopneumonia with infiltration of the walls of the bronchi and bronchioles by lymphocytes, plasma cells and large mononuclears. Masses of *Bacillus pertussis* cause matting of the cilia, but fail to penetrate below the surface. It is possible that they produce a toxin which acts on the central nervous system and especially on the nuclei of the vagus and recurrent laryngeal nerves, accounting for the paroxysmal coughing and the attacks of vomiting.

### TULAREMIA

Tularemia is another plague-like disease which affects both animals and man and is spread from the former to the latter. In animals it has the virulence and septicemic qualities of plague, but in man the infection is milder and recovery is the rule. In spite of this greater resistance man is extraordinarily susceptible to the infection. Although related to plague, the symptoms in man may closely simulate typhoid fever, and the lesions may as closely resemble those of tuberculosis. The disease is a new one, or rather a newly-recognized one. It was first observed as an acute epidemic infection among ground squirrels in Tulare County, California, and the *Bacterium tularense* was discovered to be the cause. Later it was found that the infection could be conveyed to man. At first it was thought that tularemia was a disease peculiar to the United States. Its problems have been worked out by American bacteriologists, and by Francis in particular. It is now known that it is world-wide in distribution. It is transmitted to men from a rodent, not from another man. The great reservoir of the disease is the ground squirrel and the jack-rabbit, but many other rodents are now known to harbor the infection. The domestic rabbit does not suffer from the disease. Infection is carried in three ways: (1) by biting flies, particularly the deer-fly, *Chrysops discalis*; (2) by ticks; (3) by contact with the skins or internal organs of infected rabbits. It therefore occurs in farmers, hunters, market men, butchers, housewives, and cooks. The microorganisms enter through cracks in the skin or through the eye. Laboratory workers handling and performing autopsies on infected animals are extremely liable to infection, even though alive to the danger.

Two types of the disease may be recognized in man, the glandular and the typhoid.

*Glandular Type.*—This resembles a mild form of bubonic plague, except that a local lesion develops at the site of inoculation. After an incubation period of a few days there is a sudden onset with pains, prostration and fever. The regional lymph nodes draining the site of infection become enlarged, inflamed, and tender. If the portal of infection is the eye the preauricular, submaxillary, and cervical glands are involved. Not until twenty-four hours later does a papule appear at the site of infection. Both the primary lesion and the lymph nodes undergo necrosis, suppuration, and ulceration. The bacteria have not been demonstrated in the tissues, but a bacteremia occurs early, and a positive blood culture can be obtained during the first week. By the end of the second week agglutinins appear and reach their height in the third week. After that they decline, but persist in small amounts for several years. Cross-agglutination occurs with *Brucella melitensis*, so that the disease may be confused with undulant fever. Recovery is the rule, but convalescence may take some months.

*Typhoid Type.*—Here there is no obvious primary lesion and therefore no glandular involvement. The portal of entry is unknown, but it is probably the unbroken skin, for the bacilli can penetrate the skin of the guinea-pig and set up a septicemia. The typhoid type is usually due to laboratory infection. Three cases occurred in the Lister Institute, London, being infected by a culture sent from Washington. The disease closely resembles typhoid fever, but can be differentiated by means of agglutination tests.

*Lesions.*—In man the lesions may be of two types, acute and chronic. The *acute* lesions are characterized by focal necrosis and suppuration. These changes are seen in the primary lesions and the regional lymph nodes, and to a lesser extent in many of the internal organs (spleen, liver, lung). The *chronic lesions* resemble those of tuberculosis for which they are easily mistaken. They are focal in type with central necrosis, epithelioid cells and giant cells.

*Diagnosis.*—The disease is apt to be mistaken for typhoid fever (when no primary lesion is present), for undulant fever (because of cross-agglutination), and for tuberculosis (a mistake made by the pathologist on account of the glandular lesions). When the physician thinks of tularemia on account of the primary lesion, the regional lymph node enlargement, and the history of having dressed a wild rabbit or of being bitten by a tick or fly, he can confirm his diagnosis in two ways: (1) agglutination of *Bacterium tularense* by the blood serum in the second week, and (2) isolation of *Bacterium tularense* from guinea-pigs inoculated with material taken from the primary lesion or enlarged glands or with the patient's blood. The guinea-pig will die in a week and show enlarged caseous lymph nodes and a spleen studded with tiny foci of necrosis. Smears and cultures taken from the patient are useless.

## UNDULANT FEVER

This disease, like tularemia, is an infection of animals which may be conveyed to man. Like tularemia it is in some respects a new disease, in other respects it is not. It is caused by the *Brucella* group of microorganisms named after Sir David Bruce, who first isolated them many years ago in Malta fever. The organism is a very small cocco-bacillus which has been called both a coccus (*Micrococcus melitensis*) and a bacillus (*Bacillus abortus*). It has long been known as the cause of Malta fever, an infectious disease of goats in the Mediterranean countries and conveyed to man in goat's milk. It has also been known for some time as *Bacillus abortus*, the cause of contagious abortion in cattle. The infection is extraordinarily common in cattle. Thus it has been shown that 90 per cent of the herds in Connecticut are infected. It should be noted that though the cows have a tendency to abort, and pass large quantities of the bacilli in the milk, they show no evidence of disease. The goats also suffer no inconvenience from *melitensis* infection. It was not until 1918 that an intimate relationship was demonstrated by Evans to exist between *Brucella melitensis* of Malta fever and *Brucella abortus* of contagious abortion. The two are closely related but not identical. The most important step was the last, when in 1924 Keefer showed that *Brucella abortus* was infective for man. The various forms are best included under the name of undulant fever, of which there is a *melitensis* type and an *abortus* type. The *abortus* infection may come from swine (porcine form) or cows (bovine form). The *abortus* infection is not so pathogenic for man as the *melitensis* form. Most of the persons who drink infected cows' milk show no evidence of the disease, though they may have agglutinins in the blood. Thus the morbidity for the human subject is low.

Infection is acquired *via* the alimentary tract, usually by drinking unpasteurized cows' milk, so that most human cases in temperate countries are examples of *abortus* infection. In view of the fact that this is a milk infection it is curious that the disease is rare in children. Laboratory infections may be acquired through cracks in the skin, the scratch of an infected needle, etc. Contact infection may also occur in workers in packing houses, farmers, veterinarians, and others who come in contact with infected material. The method by which infection passes from one animal to another is not certainly known. Undulant fever used to be regarded as a rarity. In 1926 only 46 cases were reported in the United States, but in 1929 over 1300 cases were reported. It is undoubtedly very much commoner than is usually thought. It should enter into the differential diagnosis of every long-continued fever when such conditions as typhoid, tuberculosis and subacute bacterial endocarditis are being ruled out. The mortality is low, less than 2 per cent. *Brucella* infection may not give rise to typical undulant fever but merely to persistent malaise and indisposi-

tion with some irregular fever. In endemic areas a certain proportion of the population suffers from a latent infection, so that the blood gives a positive reaction to the agglutination test. Women with latent infection may show a tendency to abortion.

The disease begins insidiously with an evening rise of temperature, and the patient may be ill for some time without knowing that he has any fever. Persistent weakness, muscle pains, arthritis, and marked perspiration with a peculiar sweet sickly odor to the sweat are some of the common features of a disease which may easily pass unrecognized. Orchitis is an occasional symptom. The fever may come in waves, hence the name undulant fever, though this is not common, and the infection may last for months and even years. Three months is an average duration. There is a remarkable absence of positive physical signs, owing to the general rather than the local character of the infection. The spleen is palpable in more than a third of the cases. The lymph nodes may be enlarged. A blood culture may be obtained at the height of the fever, but it is often negative, and has to be kept at least a week before any growth is apparent. The culture should be kept for five weeks before being discarded as negative. The organisms are often excreted in the urine, and a culture may be obtained from a catheterized specimen. Agglutination is the most reliable means of diagnosis. Agglutination with a titer of 1 in 100 or over in the presence of fever and the other clinical symptoms indicates active infection. A titer of 1 in 100 in the absence of clinical symptoms indicates latent infection. A titer of 1 in 80 and under in the absence of clinical symptoms indicates a past infection. Occasionally active cases fail to give agglutination, but this is uncommon. A source of confusion is a cross-agglutination with *Bacterium tularensis* which sometimes occurs.

**Lesions.**—These are very indefinite, but in general they are those of a septicemia. Very few studies of the autopsy findings in undulant fever have been recorded owing to the low mortality of the disease. The spleen is enlarged, averaging 500 grams, and there is a general swelling of the mesenteric lymph nodes. Toxic changes (cloudy swelling) are seen in the liver and kidneys. The intestine shows small areas of congestion, and swelling and edema of the mucosa. Ulcers may occur in the colon, but are not at all common. Orchitis and seminal vesiculitis are occasional occurrences, but less commonly than might be expected from the incidence of genital infection in the cow and bull. Congestion and bronchopneumonic areas are found in the lungs.

In the inoculated guinea-pig the spleen is covered with tiny caseous foci composed mainly of epithelioid cells and closely resembling the lesions of tuberculosis. In undulant fever as in tularemia the clinical picture may resemble typhoid fever while the experimental lesions in the guinea-pig simulate tuberculosis. Even in man, however, there may be granulomatous lesions consisting of epithelioid and giant cells in the liver, spleen and bone-marrow (Rabson). Parsons and his

associates claim that chronic Brucellosis of glandular type as seen in North Carolina presents a microscopic picture similar or identical with that of Hodgkin's disease; *B. melitensis* in pure culture was grown from the lymph nodes.

### SPIROCHETAL FEVERS

**Spirochætositis Ictero-hæmorrhagica. Weil's Disease.**—This is a form of infectious or epidemic jaundice caused by the *Spirochæta icterohæmorrhagica*. It is therefore considered in the discussion on jaundice in Chapter XXI.

**Relapsing Fever.**—This is a disease of tropical countries, though some cases have been reported in the United States. It is characterized by a peculiarly recurring type of fever. The febrile attacks last a few days and are separated by short periods during which the patient feels quite well. The disease is caused by several closely related species of spirochetes, of which *Spirochæta obermeieri* was the first described and is the best known. During the febrile attacks the spirochetes are present in the blood in great numbers, but during the afebrile intervals they vanish. The infection is conveyed by lice and ticks. These do not inject the organisms directly into the blood, but when the body of the louse is crushed on the surface by scratching, the spirochetes are liberated and penetrate through the skin abrasions. The mortality is not high. The postmortem lesions are those of septicemia, notably enlargement of the spleen, cloudy swelling of the internal organs, and hemorrhages in the serous and mucous membranes.

### BARTONELLA INFECTIONS

**Oroya Fever.**—This is a disease occurring in Peru characterized by intermittent fever and a severe rapidly progressive anemia, ending fatally in a large number of cases. The red blood corpuscles contain minute rod-like motile organisms first described by Barton in 1909 and known as *Bartonella bacilliformis*. A large proportion of the erythrocytes may be affected. It is now known that the fatal cases are those which are complicated by paratyphoid B infection. In cases in which paratyphoid infection has not occurred the prognosis is good, no matter how great the destruction of red blood cells.

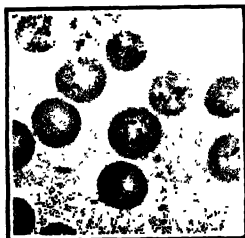


FIG. 79. — *Bartonella muris*. (McCluskie and Niven.)

Certain strains of rats may become infected with another type of *Bartonella*, *Bartonella muris*. The infection remains latent, no organisms are found in the red blood cells, but a few days after splenectomy severe and fatal anemia rapidly develops, due to invasion of the red blood cells by the *Bartonella* (Fig. 79), just as in Oroya fever. The latency appears

to be due to the inhibitory action of the reticulo-endothelial elements in the spleen.

### VIRUS DISEASES

Viruses may attack plants (mosaic diseases, etc.), possibly bacteria (? bacteriophage), animals (foot and mouth disease, distemper, vaccinia, hog cholera, etc.), and birds (psittacosis). They are responsible for a great number of diseases in man, which may conveniently be placed in the following seven groups: (1) *Skin* (dermatropic): smallpox, chickenpox, molluscum contagiosum, measles, lymphogranuloma venereum. (2) *Nervous system* (neurotropic): poliomyelitis, rabies, herpes (zoster and simplex), postvaccinal encephalitis, probably encephalitis lethargica and encephalomyelitis. (3) *Nasopharyngeal mucosa* (catarrhal): coryza, influenza, measles. (4) *Glands* (glandular): mumps, infectious mononucleosis. (5) *Proliferative*: verrucæ, molluscum contagiosum, (?) Rous sarcoma, (?) Shope papilloma. (6) *Systemic*: psittacosis. (7) *Insect vector*: yellow fever, dengue.



It is a common mistake to think that viruses are merely very minute bacteria, or that they are of a nebulous and almost theoretical character. They differ from bacteria in the following particulars. (1) *Size*. The viruses are called ultramicroscopic, but this is not strictly correct, for the largest can be seen in the form of so-called elementary bodies, and the electron microscope has brought many members of the group within the range of vision. They range in size from 5 to 30  $\mu$ . (2) *Filterability*. They can all pass through the pores of the finest unglazed porcelain filter, but this is not all-important as the name filterable virus would suggest, for many minute bacteria such as *Bacillus influenzae*, *Brucella abortus*, and most spirochetes are filter-passers. (3) *Cultural characters*. Bacteria can live on lifeless material such as gelatin and agar, but viruses can only grow in media which contain living cells. They can be grown *in vitro* (tissue culture) or *in vivo* (chorioallantoic membrane of developing chick). They are said to be cytotropic, because they appear to penetrate and live inside the cells whether in the body or in a culture medium. They do not multiply in the body fluids, and thus differ from bacteria. (4) *Specific inclusion bodies* are very characteristic of true virus diseases. We can only recognize the presence of viruses by the effects they produce—"by their fruits ye shall know them" and the most easily recognized effect is the cellular inclusion. They are not present in all, for, as Cowdry remarks, nuclear inclusions are the fingerprints of a special and limited group of viruses, and viruses, like human beings, may act without leaving fingerprints. It is doubtful if all intracytoplasmic inclusions are necessarily an indication of virus infection. The inclusions may be cytoplasmic or intranuclear; sometimes both forms are present. In some diseases, such as fowl-pox, vaccinia and psittacosis, cytoplasmic inclusions consist of aggregates of virus particles, which when dispersed are known as *elementary bodies*. In other diseases, such as rabies and yellow fever, the status of the inclusion body is uncertain. Some "inclusions," particularly intranuclear ones, may represent products of degeneration. Inclusions represent the intracellular pathology of the virus diseases. The best-known examples are the Guarnieri bodies of smallpox (Fig. 80), the Negri bodies of rabies, the Lipschütz bodies of herpes, and the molluscum bodies of molluscum contagiosum. They are also found in yellow fever, poliomyelitis, and psittacosis. Excellent illustrations of the various inclusion bodies are to be found in Cowdry's article in Rivers' book on *Filterable Viruses*. The inclusion bodies were known long before filterable viruses were dreamt of, for the molluscum bodies were described in 1841. (5) *Selective action*. To a much greater degree than in the case of bacteria viruses attack one particular tissue. Thus the virus of smallpox attacks the epithelial cells of the skin, the virus of poliomyelitis the motor anterior horn cells of the spinal cord, the virus of louping-ill (sheep) the Purkinje cells of the cerebellum. (6) *Resistance to germicides*. Although readily destroyed by heat, viruses can resist the action of substances (glycerin, etc.) which quickly kill bacteria, so that they can be isolated from material contaminated by bacteria by this means.

The nature of viruses is a matter of uncertainty. There is even doubt on so fundamental a question as to whether or not they are living, whether they are obligate parasites which require living cells for multiplication or merely the

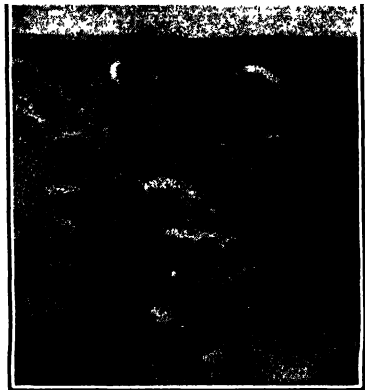


FIG. 80.—Inclusion bodies. The Guarnieri bodies of smallpox. (Kindness of Dr. J. Craigie.)

products of cellular perversion which are reproducible in series. Some may belong to one group, some to the other. Rivers sums up the matter in his Harvey Lecture: "Some viruses may be minute living organisms representing the midgets of the microbic world, others may be primitive forces of life unfamiliar to us, still others may be inanimate transmissible incitants of disease." The viruses may be situated near the line that separates inanimate, transmissible incitants from minute living organisms. The transition from one side of the line to the other may be so gradual that no great difference in the types of disease caused by agents near the line is perceptible. Stanley has obtained a crystalline protein from tobacco plants infected with tobacco-mosaic disease which has all the properties of a virus. It is still infective after ten crystallizations, and can reproduce the disease in a dilution of 1 in 1,000,000,000. Such a substance cannot be regarded as living in the ordinary sense of the word. The tobacco-mosaic virus may be considered as an autocatalytic protein which requires the presence of living cells for multiplication. Laidlaw points out that parasites lose the power of making substances which are essential to them if these can be found ready-made in the cells of the host. This laziness may be such that the power of independent metabolic activity is lost. The parasite would then be living a borrowed life, and would consist merely of nucleo-protein possessing the power of reproduction, but inanimate outside the cell. From this it will be seen that a parasite such as the tobacco-mosaic virus may have some of the characteristics of living matter and others of inanimate matter.

*Virus immunity* differs in many respects from immunity to bacterial infection. One attack of a virus disease usually confers a life-long immunity. This is true of measles, mumps, chickenpox, smallpox, herpes zoster, poliomyelitis, yellow fever, and dog distemper. The immunity seems to be due to a cellular rather than a humoral change, for although the blood of persons who have recovered from poliomyelitis contains immune bodies, these are not proportionate to the degree of active immunity produced. The immunity may also be due to a continued sojourn of the virus within the body long after recovery has taken place. Thus in the infectious anemia of horses it was found that the blood was infective as long as fourteen years after an attack. Most plants that are infected with virus diseases retain the virus as long as they live. When they recover they are immune and cannot be reinfected, but this immunity is of the non-sterile type. An anti-virus serum can be produced, but the protective substance in the serum does not appear to combine with the virus. Both the protective substance and the virus are fixed by the tissue. If fixation of the virus precedes that of the protective substance, infection of the cell is not prevented, but if fixation of the protective substance precedes that of the virus, infection is prevented. When the virus becomes fixed to the cell it is protected by the latter, and the neutralizing antiserum is unable to affect it. The immune bodies in the serum seem to act directly on the virus without the intervention of complement or leucocytes which are so essential in bacterial immunity.

The *lesions* produced by viruses are varied. There may be: (1) cellular changes, (2) inflammation, or (3) no detectable lesion. The *cellular change* is the primary one. It may take the form of hyperplasia, degeneration or lysis. The hyperplasia is marked in such lesions as verruca vulgaris (warts), molluscum contagiosum, fowlpox, the Rous sarcoma of chickens, the Shope papilloma, and the virus-produced adenocarcinoma of the frog's kidney described by Lucké. The virus evidently stimulates the cell to reproduce. Cell division is usually amitotic, but numerous mitoses may also be seen. (What relation, if any, has this to the problem of cancer?) Degeneration of the cells attacked is seen in smallpox, herpes, poliomyelitis, rabies, etc. Lysis is best seen in the phenomenon of bacteriophagy. *Inflammatory changes* occur in many virus diseases, but they are secondary rather than primary. The characteristic cell is the mononuclear or lymphocyte, no matter how acute the

disease, but there may be many polymorphonuclears, as in poliomyelitis. The central nervous system is a common site of virus diseases in man, and here the inflammatory lesions usually take the form of perivascular collections of mononuclear cells.

With this survey of the general characteristics of virus diseases, some of the examples in man will now be described.

**Smallpox.**—Smallpox or *variola* is an acute infectious fever characterized by the formation of "pocks" or pustules in the skin. Headache and persistent pain in the back are characteristic symptoms. After an incubation period of ten to twelve days the skin lesions appear and slowly develop. At first they are papules, in the course of a few days these become vesicles, and the vesicles are converted into pustules, over which scabs are formed. Healing occurs under the scabs or crusts, but when these are cast off a scar may be left. The depth of the scar depends on whether or not the destructive process has reached the cutis vera. The disease is extraordinarily contagious, the infection being conveyed by the discharge from the lesions and by the crusts. This may happen from personal contact, from contact with clothing or possessions of the patient, or by air transmission, the virus being carried on particles of dust from the scabs. Before the introduction of vaccination the disease used to be as common as measles. It was seen mostly in children, because a previous attack bestowed on adults a permanent immunity. Macaulay with characteristic rhetoric speaking of 17th Century England paints this picture: "The small pox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."

*Alastrim* is a form of smallpox met with principally in South America. It differs from smallpox in having a very low mortality, but is probably a variant of that disease due to the same cause.

**Etiology.**—Smallpox is a good example of a disease caused by a cytotropic filterable virus. The infective agent is a filter-passer, characteristic inclusion bodies are found in the local lesions, and there is a topical reproduction of the virus. The virus can be grown in artificial culture with pieces of growing skin, multiplication being shown by the result of subsequent inoculation, which is the only method of proving that a filterable virus is still active. The inclusion bodies were first described by Guarnieri, and are known as *Guarnieri bodies* (Fig. 80). They are present in the cytoplasm of the epithelial cells of the skin lesions and are easily produced by applying a small quantity of virus to a scratch in the cornea. They may be merely a degeneration product of cytoplasm, but it appears more probable that they represent some multiplying form of the virus, a colony of the minute granules which are seen in the discharge from the lesions and in vaccine lymph, and which seem to constitute the actual infective agent.

**Lesions.**—Only some of the lesions of smallpox are specific, *i. e.*, are due to the virus itself. The others are due to the secondary strepto-

coccal infection which seems to occur in every case. The streptococci are responsible for the pustular lesions, and usually for the death of the patient. The specific lesions are the papules and vesicles of the skin. The virus is epitheliotropic and multiplies in the epidermis. There is a peculiar degeneration of the epithelial cells which become swollen (ballooning) and undergo liquefaction. The change is more marked at the periphery of the lesion, so that the edges are raised, giving the center a sunken or umbilicated appearance. There is a fluid exudate in the vesicular stage, but this is clear and almost free of cells. When suppuration occurs it is crowded with pus cells. In the vesicular stage there are abundant plasma cells in the tissues, but in the pustular stage these are replaced by polymorphonuclear leucocytes. The Guarnieri bodies have already been described. The mucous membranes of the mouth and nose show the same lesions as the skin. In the internal organs there are lesions of focal necrosis (liver, kidney, heart) due to the secondary infection. Inflammatory necrotic nodules in the testicle are common. Death is often due to bronchopneumonia.

**Rabies.**—Rabies or hydrophobia is a disease affecting animals (carnivora, *e. g.*, dog, wolf) and man. The infection is transmitted to man by the bites of rabid animals, the infective agent being excreted in the saliva. The incubation period is fortunately remarkably long, usually over two months, and in rare cases as long as a year. This gives time for preventive treatment. The length of the incubation period depends on the position of the bite, being very much shorter in bites of the face and head than in bites of the leg, for a reason that will be apparent shortly. The principal symptoms are cerebral irritation, pharyngeal spasm especially at the sight of water so that the patient is unable to drink, and generalized convulsions. The disease is invariably fatal unless preventive treatment is employed.

**Etiology.**—Rabies, like smallpox, is a good example of a cytotropic virus disease. It is caused by a filter-passing agent which is neurotropic, so that the true lesion is in the nerve cells of the brain. The disease can be produced by inoculating an emulsion of the brain of a rabid animal into the subcutaneous tissue of another animal. It may, if wished, first be passed through a Berkefeld filter. As the symptoms are cerebral it is evident that the virus must pass from the site of inoculation to the brain. Like other viruses it does not travel by the blood stream, but passes along the peripheral nerves, probably along the axis cylinders, as Goodpasture has shown to be true of the virus of herpes simplex. It is for this reason that the incubation period is long for bites on the foot, short for bites on the head; it is all a question of how far the virus has to travel. Once the virus reaches the central nervous system it is rapidly disseminated throughout the brain and spinal cord.

**Lesions.**—There are no naked eye changes apart from congestion of the gray matter of the brain and cord. Microscopically there is cell degeneration, phagocytosis of the degenerating cells, and collars of inflammatory cells (lymphocytes and plasma cells) around the small

bloodvessels. The pathognomonic feature is the presence of Negri bodies. These are inclusion bodies varying much in size found in the cytoplasm of the ganglion cells in the hippocampus major as well as in the cells of the medulla, cerebellum, etc. They are acidophilic bodies with a blue center. When a dog suspected of rabies has bitten a patient, the dog's brain must be examined for Negri bodies. The most rapid method is to take a cover-glass impression of the cut surface of the hippocampus major, but a more certain method is to stain sections. The nature of the Negri bodies is still a matter of dispute, for those best qualified to judge are divided in opinion as to whether they represent aggregations of the virus or merely degeneration products of cellular origin.

*Preventive Inoculation.*—It is rather strange that the modern treatment of rabies is that introduced by Pasteur who had never heard of filterable viruses or Negri bodies. Pasteur found that the spinal cord of rabbits infected with the disease was rich in the virus, as shown by the results of animal inoculation. He also found that he could lower the virulence of the virus by the simple expedient of hanging up the cord and allowing it to dry. By drying a series of cords for varying lengths of time he obtained a series of viruses of varying virulence. Treatment is of no avail once the symptoms have manifested themselves, but Pasteur availed himself of the very long incubation period which is so striking a feature of the disease. He found that if treatment was commenced within five days of receiving the bite it was successful in nearly 100 per cent of the cases, that is to say there was complete prevention. This is surely an extraordinary *tour de force* for the earliest days of modern bacteriology.

**Yellow Fever.**—Yellow fever is an acute infection with high fever, acute nephritis, hemorrhages in the skin and from the stomach and bowels, and jaundice. It occurs in certain endemic centers in Central and South America and in West Africa which in the past have served as starting-points of epidemics. The American centers have been almost completely controlled, but that is far from being true of West Africa, where both Stokes and Noguchi died of yellow fever while investigating the disease. The mortality is above 60 per cent, but if recovery takes place a permanent immunity is established. The virus is transmitted from one person to another by a mosquito, *Stegomyia fasciata* (*Aedes ægypti*). Twelve days must elapse before the mosquito becomes infective for another person. The story of the Reed Commission which worked out the method of transmission, and of General Gorgas who waged war on the *stegomyia* and cleansed Havana and Panama of yellow fever after they had been infested for centuries, is one of the romances of medicine.

A notable advance is the discovery of an animal which can be infected experimentally. The Reed Commission had to use two of their own number as experimental animals to prove that infection was conveyed by the mosquito, and Lazear died as the result of the experiment. Stokes showed before his death that the monkey can be infected,

and all the recent work has been done on *Macacus rhesus*. It is now possible to demonstrate the presence of immune bodies in the blood of the majority of the inhabitants of some West African villages, as their blood will protect a monkey against inoculation with infected material. Moreover a vaccine has been prepared from the liver of monkeys which have recently died of yellow fever. This vaccine will completely protect a monkey from a dose of 1 gram of infected liver, although a dose of 0.0001 gram is fatal for non-immunized animals, a truly remarkable degree of immunity.

*Lesions.*—These serve to explain very completely the clinical symptoms. The virus attacks the capillaries, the liver, and the kidneys, so that there are hemorrhages, jaundice, and marked urinary disturbances. There is hemorrhage into the stomach, thus giving the “black vomit” which is so characteristic of the later stages. The intestine may be full of blood. There are hemorrhages in the myocardium, endocardium and epicardium. The most characteristic of all the lesions is the “Councilman lesion” of the liver. This is a non-inflammatory hyaline necrosis affecting many liver cells and forming a dense acidophilic mass in the cytoplasm. As the condition advances areas of necrosis are produced and the bile passages are ruptured with escape of the bile into the blood, but it is the early discrete lesion which is really characteristic. Intranuclear acidophilic inclusion bodies have been described in the liver cells in both the human and the experimental disease. (Hoffmann.) There is an extensive necrosis of the renal epithelium, so that the convoluted tubules are blocked with necrotic cells; the marked albuminuria, abundant casts, and final anuria are natural sequels, and they are among the worst prognostic signs. The spleen is of normal size, but shows a striking loss of lymphocytes. Congestion and hemorrhages in the lungs are common.

**Poliomyelitis.**—Poliomyelitis is an acute infection of the grey matter of the spinal cord and brain, and will be described in connection with Diseases of the Nervous System. As it happens to be a virus disease, some of the bacteriological features will be considered here.

The virus is an ultra-microscopic filter-passer, and is markedly neurotropic. It becomes associated with the motor cells of the central nervous system whether it is injected into the brain, painted on the naso-pharyngeal mucous membrane, or inoculated into a peripheral nerve. Like the virus of rabies, it appears to pass along the axis cylinders of the nerve until it reaches the central nervous system, where it becomes widely disseminated. The symptoms may suggest a localized infection, but the nervous lesions are always widely spread. The very important practical question of route of infection and method of spread of the disease are considered in Chapter XXXI.

Intranuclear inclusion bodies have been described by Hurst in degenerating cells in the early stage, but not when the cell has become necrotic. As in other virus diseases immunity is life-long. The blood contains immune bodies many years after the acute attack, and these may be used for the treatment of early cases.

**Herpes.**—There are two different forms of herpes, herpes simplex (febrilis, labialis, cornealis, genitalis) and herpes zoster. *Herpes zoster* follows the distribution of the spinal nerves, is accompanied by changes in the spinal fluid, and the attack is followed by permanent immunity. *Herpes simplex* is recurrent, does not follow the line of nerve distribution, and is not accompanied by changes in the spinal fluid. Both are probably virus diseases, the site of attack being the sensory nerve ganglia.

It is a remarkable fact that when the virus of herpes simplex, so harmless in man, is inoculated into the cornea of a rabbit, a fatal encephalitis is produced. Goodpasture has shown that the path of absorption is along the axis cylinders of the nerve supplying the part, whether it is sensory, motor, or sympathetic. The histological criterion for the action of the virus is the presence of Lipschütz bodies, which are intranuclear inclusions found both in the epithelial cells of the primary lesion (skin or cornea), and in the nerve cells in the brain or cord from which nerve fibers pass to the part affected. In both instances they are a proof of the direct action of the virus on the cells. The relation of herpes to epidemic encephalitis will be taken up when the latter disease is discussed in a later chapter.



FIG. 81.—Molluscum bodies lying in epidermis.  $\times 225$ .

**Molluscum Contagiosum.**—This is a contagious condition characterized by the development of small white, waxy, almost transparent raised nodules on the skin especially in children. They may last for months or years and then disappear spontaneously. Softening occurs, and a cheesy material can be squeezed out through a small opening in the skin. The condition is a true virus disease. The virus first stimulates the epithelial cells to proliferate, and hyperplasia is then followed by degeneration and softening. The characteristic feature of the lesion is the *molluscum bodies*. (Fig. 81.) These are egg-shaped glistening bodies which lie in the softened center of the lesion and can be readily extruded. If the molluscum bodies are squashed they are found to consist of an enormous number of minute granules, similar to those already described in other virus diseases, which push the nucleus to one side. The evidence in favor of the cell inclusions being intracellular accumulations of living microorganisms is stronger in the case of molluscum contagiosum than with any of the other virus diseases. When an emulsion of molluscum bodies is passed through a Berkefeld filter and injected intracutaneously into a human volunteer, typical molluscum lesions develop in the course of two or three weeks (Wile and Kingery).

**Mumps.**—Mumps or epidemic parotitis is caused by a virus which can be demonstrated in the saliva. The disease can be reproduced in monkeys by injection of a filtrate of saliva from human cases into Stenson's duct. The lesions produced by the virus are epithelial necrosis and round cell infiltration of the interstitial tissue. Inflammation of the testis (orchitis) occurs occasionally, and rare complications are acute pancreatitis and meningo-encephalitis.

**Measles.**—Measles because of its extreme contagiousness is one of the commonest diseases in the world. Yet its *cause* is still undecided. Various observers, among whom Ruth Tunnicliff deserves special mention, hold that the infective agent is a diplococcus so small that it can pass through a filter. The evidence in support of this when examined critically is suggestive but far from conclusive. It is more probable that the causal agent is an ultra-microscopic virus. The life-long immunity conferred by one attack supports this view. A second attack is extremely rare. Contagion is due to direct exposure to a case of the disease. The experimental injection of infected blood into human volunteers and monkeys has been successful in producing the disease.

The immunity following an attack of measles is associated with the presence of immune bodies in the serum, and these can be used as a means of treatment and prevention. Measles is an outstanding example of a virus disease, which can be controlled by immune serum therapy. The immune serum may prevent or modify an attack. If given within five days of contact there is complete protection, but the immunity is passive and fades in from two to four weeks. If given between the seventh and ninth day the attack is not prevented but it is very mild and gives a lasting immunity. The chief danger to life is before the fifth year, for after that the mortality is trivial. Thus before the fifth year it is better to give the serum early, but after the fifth year it is better to give it late.

The chief *symptoms* are fever, the characteristic rash, and evidence of an acute catarrhal infection of the upper respiratory tract and eyes. The commonest complication is bronchopneumonia.

**Lesions.**—As in the case of influenza, it is difficult to differentiate with certainty between the essential lesions of measles and those due to complications. Among essential lesions are those of the skin, mucous membranes of the mouth and respiratory passages, lungs, lymph nodes, and spleen, liver, and brain.

In the *skin* the chief change is a round-cell infiltration about the bloodvessels, hair follicles, and sweat glands. In the deeper layers of the epidermis there are areas of colloid degeneration of the epithelial cells passing into coagulation necrosis. These areas are surrounded by fibrin and leucocytes, and are probably due to the direct action of the virus on the epithelium.

The *mucous membrane* of the mouth and upper respiratory tract shows catarrhal inflammation. In the mouth the epithelium is thickened and in places shows foci of fatty degeneration, giving rise to the white dot which forms the center of the Koplik spot, the pathognomonic



sign of measles. The lymph follicles are swollen, and occasionally they may break down so as to form ulcers in the mouth and larynx. Warthin has described a peculiar lesion of the tonsils and pharyngeal mucosa in the prodromal stage of measles characterized by collections of multinucleated giant cells like the giant cells of Hodgkin's disease. In 3 cases he was able to make a diagnosis of measles merely from an examination of the excised tonsils several days before the appearance of the rash.

The *lungs* of fatal cases nearly always show bronchopneumonia. This should be regarded as a complication rather than as an essential lesion. If the patient recovers from the bronchopneumonia he may develop an acute form of pulmonary tuberculosis due to the lowered resistance produced by the virus.

The *lymph nodes* and *spleen* may be swollen, but never to any great extent. A peculiar giant-cell formation may occur in lymphoid tissue. This has been observed in the tonsils (Warthin) and in the appendix in the prodromal stage. Monkeys injected with blood from measles patients show giant cells in the lymph nodes (Gordon and Knighton). The spleen is seldom palpable. The *liver* often shows areas of focal necrosis. The *brain* may be the seat of a meningo-encephalitis, a lesion which will be described in connection with that disease. The *blood* shows a characteristic leucopenia, due to a diminution in the number of polymorphonuclear leucocytes. This forms a striking contrast to the leucocytosis of scarlet fever.

**Influenza.**—Influenza is the most puzzling of all the infectious diseases. It is usually the mildest of infections, lightly referred to as "a touch of the flu." At long intervals it suddenly assumes a virulent form, and like "a blast from the stars" great epidemics and pandemics sweep across the world killing millions of people. At such times, as in the 1918-1919 pandemic, it seems that "the Angel of Death is abroad in the land; you can almost hear the beating of his wings." During that pandemic 500,000,000 were attacked and 15,000,000 were killed. Are these two diseases the same although of different intensity? It is hard to say, because we have no criterion by which influenza can be recognized with certainty apart from its epidemic character. There is no infallible clinical symptom, no certain laboratory test, no pathognomonic autopsy lesions.

**Etiology.**—The etiology of influenza has long been the subject of controversy, an excellent summary of which will be found in a review by Holman. At the end of the great pandemic of 1889-1892 Pfeiffer found a minute Gram-negative hemophilic bacillus in the sputum and bronchial passages of influenzal patients, and concluded that this must be the cause of the disease, so that it became known as *Bacillus influenzae*. It has now been established that epidemic influenza is caused by a virus, or rather by at least two viruses, A and B, of which A is by far the commoner; B has only been found in small isolated outbreaks. The two viruses are perfectly distinct, as shown by neutralization tests with immune serum. None of the ordinary laboratory animals are sus-

ceptible to direct inoculation from man, but in 1933 Smith, Andrewes and Laidlaw showed that ferrets are susceptible and also swine. After passage through the ferret white mice can be infected by instillation into the nostrils. Ferret infection is contagious whereas mouse infection is not. The explanation of the difference is simple; the ferret sneezes and the mouse does not. Pneumonia only occurs after either anesthesia or after repeated passage through ferrets. The solid lung is bacteriologically sterile, but rich in virus. The virus responsible for the great 1918 pandemic can no longer be isolated from man. It has vanished. It used to be believed that the virus passed into swine, causing the swine influenza which appeared in 1918, and that it survives in swine though dying out in man. Unfortunately this pretty theory has now to be abandoned. The cause of endemic influenza, commonly called gripe, has not yet been determined. It is apparently not due to either the A or B virus of epidemic influenza.

The virus can conveniently be grown on the allantoic membrane of the developing chick by inoculating through a small drill hole in the shell of the egg. Hirst, and independently McClelland and Hare, have shown that the presence of virus in the allantoic fluid can be recognized by the fact that such fluid agglutinates chick red blood cells.

The part which other organisms may play in association with a virus is well illustrated by Shope's work on swine influenza. This disease can be produced experimentally in pigs by means of a filterable virus acting in conjunction with *Hemophilus influenzae suis*, a small hemophilic organism which is present in the natural disease, but is quite unable to induce the disease by itself when inoculated intranasally. The virus alone was unable to produce the typical disease, but did cause an exceedingly mild infection which was contagious. The combination of the comparatively innocent virus and a culture of *H. suis* produced severe and typical lesions, so that it appeared as if the virus conferred powers of invasion on *H. suis*. Some such co-ordinated mechanism may be at work in human influenza.

*Lesions.*—The lesions of fatal cases of influenza will be described in connection with diseases of the respiratory system. It may be said here that in all cases the essential lesion seems to be an acute inflammation of the upper respiratory tract, commencing in the nasopharynx, affecting the sphenoidal and other air sinuses, and passing down to cause a tracheobronchitis. Patches of interstitial pneumonia with mononuclear collections in the bronchial walls similar to those already described in measles form a characteristic feature. The influenzal pneumonia with great hemorrhagic edema in the pulmonary alveoli which is so frequently seen at autopsy is probably due to secondary invaders.

*Psittacosis.*—This is another disease of animals occasionally transmitted to man. It is a disease of South American parrots and parakeets (*psittakos*, parrot), often known as parrot fever, and when a pandemic occurs among the birds, small epidemics are certain to appear in the countries to which the parrots are exported. Canaries and finches in contact with parrots may

acquire the infection. Man to man infection may occur, but is not common. The last notable epidemic occurred in 1929-1930 in many parts of Europe and America, but even in epidemic periods the disease is really rare. It is extremely infective for laboratory workers investigating the disease, even though they have not come in actual contact with diseased parrots. The virus is present in the nasal discharge and feces of infected birds, contaminates the air in the vicinity of the cages, and is inhaled by persons in the vicinity.

The onset is sudden with fever, intense headache, gastro-intestinal disturbance, and a clinical picture often mistaken for typhoid fever. The physical signs, on the other hand, are those of an atypical pneumonia. There is consolidation and cough, but no sputum, pleurisy or leucocytosis. The presence of a parrot in the history is necessary for a positive diagnosis. The mortality in the English cases was 20 per cent. There is a reliable complement fixation test, but it is also positive with the serum in lymphogranuloma venereum; the Frei reaction is also positive in psittacosis.

For long it was thought that a bacillus of the paratyphoid group, first described by Nocard and known as Nocard's bacillus or *Bacillus psittacosis*, was the causal agent. It was shown in 1930, however, that the agent was a filterable virus.

**Lesions.**—The chief lesions are in the lungs. There is a patchy pneumonia, but with very little fibrin in the exudate and no fibrinous pleurisy. The really characteristic lesion, however, is a remarkable swelling of the epithelium lining the alveoli and a proliferation of the cells as indicated by numerous mitotic figures. The proliferated cells may become desquamated and form characteristic clumps and plugs in the alveoli. Apart from this the human lesions are not characteristic, for they are very varied, due probably to secondary infections. In inoculated mice foci of necrosis are found in the spleen and liver. The bronchioles are filled with an exudate which blocks the lumen and causes areas of collapse to be formed. Rickettsia-like inclusions have been described in the endothelial cells of the lung, liver and spleen in parrots which have died of the disease. Other lesions in the body are a moderate degree of enlargement of the spleen and congestion of the internal organs.

## RICKETTSIA DISEASES

In 1909 H. T. Ricketts described minute bodies in the blood of patients suffering from Rocky Mountain fever and in the tick which carries the disease. In 1910 Ricketts and Wilder found the same minute bodies in the intestinal canal of lice which had fed on typhus patients. These are now known as Rickettsia bodies or simply Rickettsia. They are just visible, being from 0.3 to 0.5 micron in diameter. Their filterability is doubtful. They vary in shape, and stain best with Giemsa. It is now known that there are many different varieties of Rickettsia. They are all transmitted to man by some insect (arthropod) vector. They grow only in the cytoplasm of living cells, not on artificial culture media; for this reason typhus vaccine is grown on the yolk-sac of developing hen's eggs. In man they live only in the mesothelial cells of the vascular and reticulo-endothelial systems. They cause a cutaneous rash, and nervous and mental symptoms. The serum of patients contains agglutinins for the Proteus group of bacteria. They develop in the gut of the arthropod host, multiply there, and are discharged in enormous numbers in the dejecta. Only three are known to be pathogenic for man, causing typhus fever, Rocky Mountain spotted fever, and trench fever.

**Typhus Fever.**—Typhus is an acute infectious fever which used to be one of the great scourges of man. Being carried by the body louse it is seldom seen in ordinary life, but was fearfully prevalent during the World War, especially in the Balkan States. No disease has been more fatal to the men who have investigated it. Ricketts, Prowazek, Bacot, and many others are among its distinguished victims. Although many microorganisms have been described in connection with typhus, there seems to be little doubt that it is

caused by a *Rickettsia* body, *Rickettsia prowazeki*, which is found both in the human patient and in the lice which have been feeding on him.

Zinsser, in his delightful and entertaining *Rats, Lice and History*, remarks that "louse transmission was the great discovery made by Nicolle, which furnished the first powerful weapon for a counter-attack against the disease. It explained the manner in which epidemics are propagated. It removed all mystery from the historic association of typhus epidemics with wars, famines, and wretchedness. But it left unanswered the problem of the smouldering embers of the virus in interepidemic periods." For the human louse soon dies on being infected with typhus. The secret reservoir of infection was only recently found to be the domestic rat, transmission from animal to animal being through the agency of the rat flea. If the rat dies and the rat flea is hard put to it to find a new host he may bite man. This is the sporadic case. If the victim is lousy and lives in a lousy community, the result is an epidemic.

The onset of the disease is acute, with high fever, great weakness and prostration, tracheobronchitis with bronchopneumonia, and a macular rash which is often characteristically hemorrhagic. There may be necrosis of the skin.

*Lesions.*—The gross pathological changes are not characteristic. There is acute splenic swelling and cloudiness of the organs. The *microscopic changes* are quite characteristic, taking the form of proliferative and thrombotic lesions in the vessels of the skin, the skeletal muscles, the heart, and the central nervous system. It is these which are responsible for the hemorrhagic rash and the occasional necrotic lesions. There is a swelling and proliferation of the vascular endothelium, and at the site of this swelling thrombosis is liable to occur. In Giemsa preparations the swollen endothelial cells may sometimes be seen to be crowded with *Rickettsiæ*. Perivascular accumulations of mononuclear and polymorphonuclear cells are common, and in addition tubercle-like nodules are scattered through the central nervous system. These are produced by neuroglial proliferation, and provide another example of the proliferation which is so characteristic a feature of the microscopic lesions.

In man the *Rickettsiæ* are found in the endothelial cells. In the louse they are confined to the lining epithelium of the gut, where they multiply prodigiously. Beautiful illustrations of the lesions and the *Rickettsia* will be found in Wolbach's monograph. Infection is carried by the body louse, which does not become infective until seven days after feeding. The infection is not necessarily caused by bites, for the excreta of the louse is swarming with *Rickettsia*, and these, when deposited on the skin, may enter through scratches and abrasions. Bacot died of typhus although he was never bitten. The virus is present in the blood, in the leucocytes and in the blood platelets. It is often stated that it is filterable, but this is probably a mistake. The disease can be transmitted to monkeys and also to guinea-pigs by the subcutaneous injection of infected blood and by the bites of infected lice.

The *Weil-Felix reaction* is a curious example of heterologous antibody action. The blood of typhus patients gives a marked agglutination with many coliform organisms, and particularly with the *Proteus* group. This *Bacillus proteus* reaction is positive by the fifth day in 50 per cent of cases, and soon becomes positive in over 90 per cent of cases. It is therefore of great diagnostic value. Though described by Weil and Felix in 1916 it was previously described by Wilson of Belfast in 1910.

*Tsutsugamushi Fever.*—This typhus-like infection, also known as scrub typhus, is endemic in Japan, Malaya and the East Indies. It is caused by *Rickettsia orientalis*, and the disease is transmitted by the bite of an infected larva of certain mites. The habitat of the mite is in rotting vegetation and tall grass, hence the name scrub typhus. Indeed it would be better called mite typhus, just as we may distinguish louse-borne typhus (ordinary typhus), tick-borne typhus (Rocky Mountain spotted fever), and flea-borne typhus. Only in louse-borne typhus is the infection transmitted directly from man to

man. A characteristic ulcer usually develops at the site of entry of the infection, associated with local and general lymphadenopathy.

**Rocky Mountain Spotted Fever.**—Rocky Mountain fever or spotted fever bears a remarkable resemblance to typhus fever in regard to symptoms, lesions, and bacteriology. It is an acute infection with headache, continued fever, pains in the muscles, and a macular eruption which often becomes hemorrhagic ("spotted fever"), and sometimes necrosis of the skin. It used to be thought that the disease was confined to the northwestern part of the United States (Rocky Mountain region), but it is now known that the infection may be acquired over a considerable part of the United States, east as well as west, and in southern Canada. There is some difference between the lesions in the eastern and western forms of the disease.

The disease is caused by one of the *Rickettsia* group, and is therefore conveyed by an arthropod, this time a wood tick, *Dermacentor venustus*. The disease is confined to regions and seasons (spring and early summer) in which wood ticks abound. As in the case of typhus, laboratory workers may acquire the disease without being bitten by the tick. In such cases the infected material must get on the skin and penetrate through cracks and scratches. The infection can be transmitted to the monkey, rabbit, and guinea-pig. In the guinea-pig the disease is much more severe than when the animal is infected with the *Rickettsia* of typhus, and there is often necrosis of the external genitals. The organism has never been cultivated on artificial media, nor is it filterable. It is always intracellular in the tick. Unlike *Rickettsia prowazeki*, it can be transmitted from one generation of tick to another without the intervention of man. Washed red and white blood cells can transmit the disease to an animal, although *Rickettsiæ* are almost never seen within these cells, suggesting that the virus may assume a form in which it cannot be demonstrated at present. A vaccine has been prepared from an emulsion of infected ticks. By its use (dose = 4 ticks) the mortality in the Bitterroot Valley, Montana, has been reduced from 90 per cent to 9 per cent.

**Lesions.**—These are very similar to those of typhus fever. The spleen is enlarged, and there may be hemorrhage in the ovaries and testes, but the only characteristic lesions are microscopic. There is the same proliferative arteritis combined with thrombosis. The endothelial cells lining the vessels become greatly swollen and undergo division. Thrombosis, both mural and occluding, occurs on the swollen endothelium. The result of the vascular occlusion is seen in the hemorrhagic rash and the necrotic areas on the skin. In the eastern form of the disease focal brain lesions consisting of axonal swelling and degeneration, together with a proliferative gliosis, are very characteristic; they are never found in the western form. (Lillie.)

**Trench Fever.**—This is the third of the *Rickettsia* diseases, but differs from typhus fever and Rocky Mountain spotted fever in having a mortality so low that nothing is known of the lesions in man. The infection is carried by the body louse, so that the disease affects troops under conditions of trench warfare. It was the commonest of all the diseases affecting the British army in France. It is an acute febrile disease characterized by great prostration, severe pain in the muscles and bones ("shin bone fever"), and recurring attacks of fever often at intervals of five or six days ("intermittent fever," "five-day fever"). Pain in the muscles is severe and very characteristic. In many cases there is a red macular rash. It will be seen that the symptoms are not unlike those of typhus and Rocky Mountain spotted fever. A striking feature is the long period during which the patient harbors the infection. Lice have been infected from a patient more than a year after the onset of the disease. The recurrences which sometimes occur many months after the initial attack are thus easy to understand.

Infection can be transmitted from one person to another by the injection of whole blood or of washed red or white corpuscles, but not by the use of

serum. The infection is therefore carried in the cells. The *Rickettsia* are found in lice which have fed on trench fever patients. The organisms are present in enormous numbers in the excreta of the louse. Infection is due either to bites or to excreta being rubbed into scratches and abrasions.

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## CHAPTER VIII

### DISEASES CAUSED BY ANIMAL PARASITES

**PATHOGENIC** parasites are of common occurrence even in temperate countries, and when the tropical parasites are included we meet some of the most widespread diseases of mankind. Many of the parasites pass through a complicated life cycle, which adds to the interest (and the difficulty) of the subject. Very few parasites pass their life cycle in only one host. The eggs produced in the body of a man or animal do not develop in the same body. They may develop into larvæ in the soil, or they may be ingested by another host and develop there. The *definitive host* is the host of the adult parasite (sexual cycle), and the *intermediate host* is the host of the embryo (asexual cycle). Thus man is the definitive host of the common tapeworms, but the intermediate host of the malarial parasite. A *vector* is a means of conveying parasites to a new host; vectors may be vegetable or animal foodstuffs or insects. An insect vector may also be a host. A knowledge of the life history of the parasite outside as well as inside the patient is essential if the disease is to be attacked rationally and successfully.

The teacher of pathology commonly finds that the student experiences great difficulty in mastering the subject of the animal parasites, for which he is apt to acquire a marked distaste. This is because he is overwhelmed by the number of parasites and the need of learning the exact dimensions of the male and female of each species. For this reason only a limited number of parasites will be described here, and emphasis will be laid on their biological behavior and the disturbances they produce in man rather than on their structural details. The latter can be obtained in any book on parasitology.

The subject will appear less vast and confusing if the beginner will realize the following facts. Disease-producing parasites belong to two great groups, protozoa (unicellular organisms) and worms. There are four important protozoal parasites, causing malaria, Leishmaniasis, trypanosomiasis, and amœbic dysentery. The worms are divided into flukes, tapeworms and round worms. Of these one fluke will be considered, four tapeworms, and six round worms. A wealth of information and superb illustrations will be found in the *Atlas of Pathology of Tropical Diseases* by Ash and Spitz.

#### PROTOZOA

**Entamoeba Histolytica.**—This is the cause of amebic dysentery, which is considered in connection with diseases of the intestine. The ameba is a single cell from 20 to 30 microns in diameter, with an outer

hyaline ectoplasm and an inner granular endoplasm. Movement is effected by an outflowing of the outer hyaline zone in the form of pseudopodia into which flows the granular endoplasm. The parasite is recognized by its mobility, which can be studied in an absolutely fresh specimen of feces on the warm stage of the microscope. Differentiation from the harmless *Entamoeba coli*, which also occurs in the stools, is difficult; *Entamoeba histolytica* frequently contains red blood cells and vacuoles, whereas *Entamoeba coli* does not. In chronic cases, such as are seen in temperate countries, there are often no mobile forms, for under unfavorable conditions the ameba becomes globular, shrinks in size and is converted into a cyst measuring 10 to 15 microns and having an outer capsular layer. The cystic forms of *Entamoeba histolytica* and *Entamoeba coli* are much more easily differentiated than the active forms, for the former cysts have four nuclei

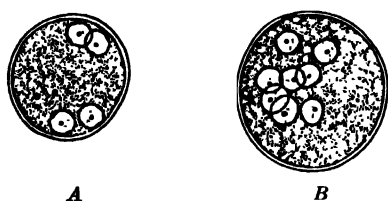


FIG. 82.--A, Cyst of *E. histolytica* stained with iodine, showing 4 nuclei; B, cyst of *E. coli* with 8 nuclei. (Blacklock and Southwell, Human Parasitology, H. K. Lewis & Co.)

when fully developed, the latter have eight nuclei. (Fig. 82.) In an unstained specimen the cysts of *Entamoeba histolytica* usually show characteristic rod-like structures called chromidial bars. The cysts are round, hyaline and easily overlooked. They are readily demonstrated by mixing the stool with Gram's iodine, which shows up the nuclei as colorless rings but not the chromidial bars. The nuclei

can be even better shown by staining a fixed smear with iron hematoxylin. Many errors are made in naming the ameba in liquid stools where it occurs in active form. It is best to look first in a liquid stool (after a saline cathartic); if there are amebæ and no cysts, wait for identification of the cysts in a formed stool. The cysts are the infective form of the parasite, for the active form is killed by the gastric juice as it passes through the stomach. Multiplication is by direct division; there is no sexual stage.

The ameba is arrested in the colon, where it may invade the mucosa and set up the acute inflammation of dysentery. From the intestine it may invade the radicles of the portal vein, be carried to the liver, and there give rise to amebic abscesses. The disease is spread from person to person and by flies. While fly infection must be guarded against in the country, in the city the chief danger is from food handlers who are chronic carriers, and in whose stools the cysts may be found. Amebic dysentery is endemic in the tropics, but isolated cases and occasional epidemics occur in England, the United States, Canada, etc. These can usually be traced to food carriers. Intestinal amebiasis is a common condition; indeed it is estimated that 10 per cent of the population of the United States (3 per cent in large cities) harbor *Entamoeba histolytica* in the intestine. But we must distinguish between amebiasis and dysentery. As Lynch remarks: "Amebic

dysentery is the comparatively uncommon acute phase or end-result of intestinal amebiasis." It is not known what upsets the usual balance between parasite and host.

**Balantidium Coli.**—This is a ciliated protozoön parasite which, like *Entamoeba histolytica*, occurs in the bowel in an active or trophozoite form and in an encysted form. The cysts are passed in the stools and are infective, while the active form dies outside the body. In the intestine the encysted parasites develop into trophozoites, which invade the mucous membrane and produce ulcers, chiefly in the large intestine, but occasionally in the lower part of the small intestine. The ulcers resemble those of amebic dysentery, and the symptoms are dysenteric in type.

**Plasmodium Malariae.**—The malarial parasite was discovered by Laveran in 1880, and in 1895 Ronald Ross showed that the disease was transmitted by the anopheles mosquito. These are the two great landmarks in the fight against one of the most important diseases which afflict man. The word malaria is of interest. It means bad air (*malo*, bad; *aria*, air), and is a reminder of the days when the disease was thought to be transmitted by the miasmatic vapors of marshes; it was the mosquitoes that lived in the marshes. Among all tropical diseases malaria is supreme. It is the most persistent, the most destructive, the most widespread, and the most difficult to control. Osler, indeed, has called it the greatest single destroyer of the human race. Those peoples touched by the shaking finger of malaria have undergone a gradual decadence, as may be seen in the history of Greece and Rome.

There are three forms of malaria: benign tertian caused by *Plasmodium vivax*, quartan caused by *Plasmodium malariae*, and malignant tertian or subtertian caused by *Plasmodium falciparum*. The third form is also known as estivo-autumnal, because in subtropical countries it occurs principally in the later summer and autumn. In benign tertian the characteristic chill or attack of fever occurs every forty-eight hours (every other day) and lasts only two or three hours, in quartan it occurs every seventy-two hours (every third day), and in the malignant tertian it occurs every forty-eight hours but is prolonged for several hours with a plateau rise of temperature making the attacks seem closer together. The distribution is as wide as that of the anopheles mosquito; it embraces the tropics, the southern United States, and many parts of Italy, Greece, the Balkans, etc. The modern treatment of general paresis of the insane by injecting the malaria parasite has brought the disease before the physicians of colder countries. The disease may recur after one or several years, for the parasites hide in the spleen and bone-marrow, and come out when the patient goes to a cold climate. The parasite passes an asexual stage of its life cycle in man and a sexual stage in the mosquito. (See Plate IV.)

**Asexual Stage.**—The tertian, the commonest form, will be taken as an example. When an infected mosquito bites a man it injects a large number of rod-shaped parasites known as *sporozoites* or spores into the blood stream. One sporozoite attaches itself to an erythrocyte, pene-

trates it, becomes rounded, and enters on the stage of asexual development. A multitude of names have been given to the various steps of the process by zoölogists, but these will be omitted for the most part. The parasite, being a cell, consists of a nucleus and cytoplasm. It forms a rounded body within the red blood corpuscle, the nuclear chromatin staining red with Wright's stain and the cytoplasm blue. The parasite often assumes a signet-ring form, with red nucleus at one side of the ring. The parasite grows rapidly at the expense of the hemoglobin, so that the red cell becomes pale and swollen. The parasite contains dark brown granules of pigment derived from the hemoglobin and commonly called malarial pigment. The pigment is manufactured by the parasite, and does not give the reaction for hemosiderin. The cytoplasm of the erythrocyte shows a fine red stippling (Schüffner's dots) which is not seen in the quartan and estivo-autumnal forms (see colored plate). Asexual division then occurs. The nuclear chromatin divides into 18 or 20 fragments (in the tertian type), and the cytoplasm is divided so as to surround each of these. The new bodies are arranged around the periphery of the erythrocyte to form a *rosette*. The rosette breaks up into a number of new individuals or *merozoites*, and at the end of forty-eight hours these are discharged from the ghostly remains of the erythrocyte into the blood stream. This process is repeated in all the infected erythrocytes at practically the same time, and it is the sudden

#### EXPLANATION OF PLATE IV.<sup>1</sup>

Partly schematic. Drawn and rearranged by Williams, partly from Muir and Ritchie, partly from Kolle and Hetsch and partly original. Giemsa's stain.

The asexual forms show cycle of the organism in the red blood cells of the human host. They show schematically the time of fever and the day of segmentation.

##### *Tertian type.*

FIG. 1.—Segmented organism.

FIG. 2.—Young ring form in cell and a young form on surface.

FIG. 3.—Growing schizont; irregular form due to great motility; beginning pigment formation; red blood cell becoming paler.

FIG. 4.—Larger schizont. Red cells pale and stippled (Schüffner's dots).

FIG. 5.—Nucleus divided into four clumps.

FIG. 6.—Further division of chromatin and formation of irregular rosette. Pigment finely granular in center.

FIG. 7.—Segmentation. Note 18 merozoites (usually 16).

*Quartan type.* Shows following differences from tertian: Slightly larger, fewer segments (usually 8), and more regular. Pigment coarse. Red blood cells unaltered. Segmentation every seventy-two hours.

*Malignant tertian type.* Shows following differential points: Merozoites smaller and more numerous (32); organism less motile with less pigment. Red blood cells smaller and greenish color (in fresh cells).

Sexual forms. Show cycle of development in mosquito.

FIG. 1 (A to E).—Male (♂) and female (♀) forms of tertian type formed in human blood; F, flagellation of male type in stomach of mosquito; G, H, changes in female type and fertilization in stomach of mosquito.

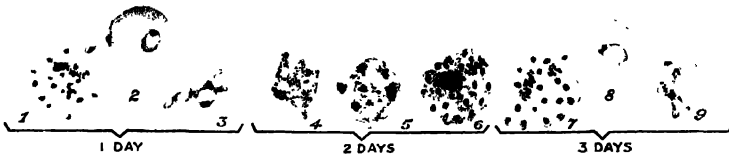
FIG. 2.—Development of sporocyst within mosquito. Liberation of sporozoites which find their way to the salivary gland.

FIG. 3.—Sexual forms of malignant tertian type found in human blood, showing development of sickle-shaped bodies.

<sup>1</sup> From Park and Williams: Pathogenic Microorganisms.

# PLATE IV

## A. PLASMODIUM VIVAX



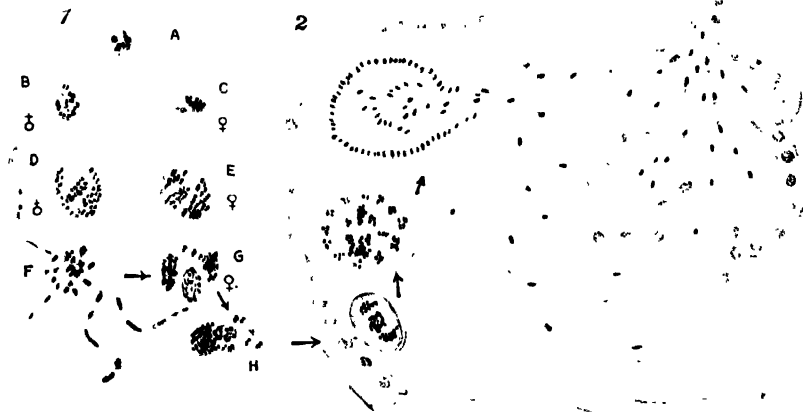
## B. PLASMODIUM MALARIAL (QUARTAN)



## C. PLASMODIUM FALCIPARUM



## D. DEVELOPMENTAL CYCLE IN THE MOSQUITO



## E. SEXUAL FORMS OF PLASMODIUM FALCIPARUM





outpouring of foreign protein into the blood which is the cause of the chill and fever. Each merozoite now becomes attached to and enters a fresh erythrocyte, and the whole process is repeated. It is evident that a profound anemia may be produced in this way.

*Sexual Stages.*—Some of the merozoites develop into parent sexual cells or *gametocytes* which are set apart for sexual reproduction. In the malignant tertian type these have a characteristic crescentic form. If the gametocytes are taken into the stomach of the female anopheles mosquito they enter upon the sexual stage of the life cycle. The gametocytes are male and female. From the male gametocytes are protruded a number of whip-like bodies resembling spermatozoa. These are detached and form the *male gametes*. The female gametocyte loses some nuclear chromatin and becomes the *female gamete*. One male gamete then enters a female gamete and conjugation takes place. The impregnated cell is called a *zygote*. The *zygote* burrows through the epithelium of the gut and forms a cyst within which the nucleus divides into hundreds of rod-like bodies, the *sporozoites*. The entire process occupies about twelve days. The sporozoites make their way to the salivary glands, and when the mosquito bites a person they are injected into the blood stream, where the asexual cycle is once more repeated.

The sexual cycle is needed for the rejuvenation and continued existence of the parasites. But without the assistance of this phase they may live in the internal organs (chiefly the spleen) of the patient for months or even years without giving rise to symptoms. He may move to a temperate country where there are no mosquitoes, quite unconscious that he is still a sufferer from the disease. Then an exposure to cold or some lowering of the vitality may bring on a typical pyrexial attack with numerous parasites in the peripheral blood stream.

*Morbid Anatomy.*—At autopsy the two most striking changes are a slate-colored or blackish pigmentation of the abdominal organs and great enlargement of the spleen. The discoloration is due to malarial pigment which resembles melanin in color. It contains iron but does not give the Prussian blue reaction. The spleen is very large, and in acute cases it is extremely soft and diffuent, but in chronic cases it becomes very hard. Microscopically the parasites are seen in the capillaries and there are great deposits both of malarial pigment and hemosiderin. In the occasional acutely fatal case the capillaries are stuffed with parasites. This is best seen in the brain, where the condition may be responsible for coma. Microscopically there is widespread vascular injury, evidenced by fatty degeneration of the endothelium, ring hemorrhages in the brain, and hemorrhagic necrotizing lesions in the myocardium, adrenals, etc. The capillaries of the brain are stuffed with parasitized red corpuscles (Fig. 83), a condition which may result in coma. A fundamental feature of the disease is a marked slowing of the capillary circulation, especially in the brain. This is due to an altered physical quality of the parasitized red corpuscles, which, particularly in the subtertian form, become

sticky and adhere to the vessel walls. As a result of this the red cells become agglutinated and form capillary thrombi. There is moreover "blocking" of the reticulo-endothelial system by the liberated pigment. The pigment deposits are most marked in the spleen, liver, and bone-marrow, much of the pigment being within the swollen reticulo-endothelial cells of these organs. In the late stages the spleen may be greatly fibrosed. The enlarged spleen may be ruptured even by slight trauma, a point of medico-legal importance.

**Blackwater Fever.**—Blackwater fever is a complication of malignant tertian malaria characterized by the passage of red or almost black urine. In severe cases death is the rule. There is a rapid and massive destruction of red blood cells, which may fall as much as 2,000,000 in number in twenty-four hours. The result is hemoglobinemia, hemoglobinuria, intense jaundice, anuria, and frequently death. Methemoglobin is responsible for the very dark color of the urine. The spleen is greatly enlarged, bright red and velvety. The administration of quinine may precipitate an attack. Blackwater fever appears to be an allergic response to reinfection with the parasite of malignant tertian.

Most people develop a certain degree of immunity, but a few become allergic. Injection of a suspension of ground-up parasites into the skin of such persons produces an allergic reaction. Quinine liberates the allergen from the parasites. The acute manifestations are in the nature of anaphylactic attacks.



FIG. 83.—Parasitized red cells in capillaries of the brain.  $\times 1000$ .



FIG. 84.—*Trypanosoma gambiense*.  $\times 1500$ .

**Trypanosomes.**—Trypanosomes are spindle-shaped protozoan parasites characterized by a macronucleus and a micronucleus, an undulating membrane, and a flagellum. (Fig. 84.) They therefore belong to the group of the flagellates, and vary in length from 10 to 30 microns. The macronucleus is in the center of the parasite, while the micronucleus is a small mass of chromatin at one end. The undulating



membrane is a wavy structure which runs like a fin along the length of the parasite. The flagellum arises from the micronucleus, passes along the undulating membrane, and is prolonged as a free structure which waves about so that the parasites are actively motile. Sexual development occurs in an invertebrate host, the tsetse fly, which transmits the infection from one person to another. Asexual reproduction is by means of longitudinal division in the blood of the intermediate host, *i. e.*, man and many wild animals. There are many varieties of trypanosomes and many tsetse flies, but only two are concerned in the production of serious disease. Trypanosomiasis, the disease caused by trypanosomes, is confined to tropical Africa.

**Animal Trypanosomiasis (Nagana).**—This is caused by *Trypanosoma brucei* (named after Sir David Bruce who discovered it), and the intermediate host is the tsetse fly, *Glossina morsitans*. The wild animals (deer, etc.) act as a reservoir for the infection, although they suffer no symptoms, but when domestic animals (horses, cattle) are taken into the fly belt they are at once infected and the disease is extremely fatal.

**Human Trypanosomiasis (African Sleeping Sickness).**—The human disease is caused by *Trypanosoma gambiense* (called after the Gambia River in which district the fever is prevalent), and is carried by the tsetse fly, *Glossina palpalis*. The trypanosomes live in the blood, causing fever, weakness, emaciation, and enlargement of the cervical and other lymph nodes. It is only later that they invade the central nervous system and cause true sleeping sickness with its characteristic lethargy and coma. The trypanosomes are found in the blood during attacks of fever, in the lymph nodes at any time, and in the cerebrospinal fluid when symptoms of sleeping sickness have developed. The brain lesions are foci of round-cell perivascular infiltration much like those of general paresis of the insane.

**Chagas' Disease.**—Chagas' disease is a form of trypanosomiasis occurring in South America. Unlike the African form these trypanosomes (*Trypanosoma cruzi*) penetrate the tissue cells, lose their flagellum, and develop into round leishmania-like bodies about 4 microns in diameter which divide repeatedly and fill the cell. After this intracellular multiplication the rounded bodies develop a flagellum and emerge in the circulation. Various bugs constitute the definitive host. The symptoms of Chagas' disease depend upon the organs the cells of which are penetrated by the parasites, *e. g.*, heart, brain (neuroglia cells), kidney, adrenal, thyroid. The general symptoms include anemia, enlarged lymph nodes, and fever.

**Leishmaniasis.**—This tropical disease is caused by the *Leishmania* group of flagellates, *i. e.*, a parasite which may lose its flagellum and develop into a small, round or oval body about one-half the size of a red blood cell, containing two nuclear bodies, one much smaller than the other, which stain red with the Leishman and other Romanowsky stains. Only the leishmania form occurs in man, the flagellate form being found in the gut of certain insects which have fed on an infected patient, or in culture of his infected blood. Leishmaniasis occurs in two clinical forms, visceral and cutaneous.

**Visceral leishmaniasis**, commonly known as *kala-azar*, is caused by *Leishmania donovani*. It is characterized by extreme enlargement of the spleen, moderate enlargement of the liver, progressive anemia and marked leuco-

penia. It is one of the most important causes of splenomegaly in the tropics. The disease is prevalent among children and young adults in India, China, and the Mediterranean countries. The parasites crowd the reticulo-endothelial cells of the spleen, liver, and bone-marrow, but are extremely difficult to find in the blood. They are readily demonstrated in smears made from a splenic puncture, being both intracellular and extracellular. (Fig. 85.) The parasites develop in the gut of the sand-fly (*Phlebotomus*) but it is not certain what part that insect plays in conveying infection. Smears from the nasal cavities and tonsils of patients show Leishman-Donovan bodies, the tonsils being massively infected. This is probably an important method of transmission, perhaps the most important.

*Cutaneous leishmaniasis*, known also as oriental sore, Delhi boil, Aleppo boil, etc., occurs not only in the regions where the visceral form is prevalent, but also in Central and South America. The parasite is morphologically and culturally identical with *L. donovani*. The lesion, which is generally single, takes the form of a chronic sore which heals spontaneously in the course of a year. It consists of a dense accumulation of histiocytes which contain large numbers of Leishmania.

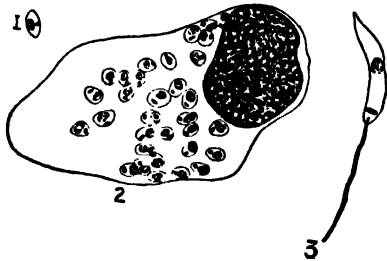


FIG. 85

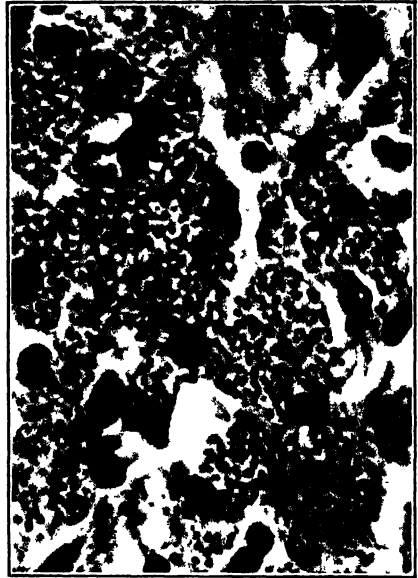


FIG. 86

FIG. 85. —Leishmania. 1, Individual parasite; 2, mass of parasites in a macrophage; 3, flagellate form. (Blacklock and Southwell, Human Parasitology, H. K. Lewis & Co.)

FIG. 86. — Reticulo-endothelial cells of lymph node packed with histoplasma capsulatum.  $\times 510$ . (From a section of Dr. W. A. D. Anderson.)

**Histoplasmosis.**—This is a rare, usually fatal fungus infection caused by a yeast, *Histoplasma capsulatum*. The organism is of about the same size and appearance as the Leishman-Donovan bodies of Kala-azar, but it is a fungus, not a protozoön. In the body the fungus occurs as a yeast-like form; when grown outside the body it assumes a mycelial form. It has never been found occurring naturally outside the body. The disease was first described by Darling in 1906, and the titles of his two papers summarize many of the essential features: "A protozoön general infection producing pseudo-tubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes," and "A fatal infectious disease resembling kala-azar." The lesions, which are widespread anatomically, are granulomatous in type, sometimes tubercle-like, with areas of necrosis. The reticulo-endothelial cells, which are greatly swollen, are crowded with parasites (Fig. 86), and the mononuclear cells of the peripheral blood may show a similar appearance. A diagnosis may be made from biopsy of a lymph node, and the fungus can be cultured from the blood. Fever,

anemia, leucopenia and *splenomegaly* are prominent features of the clinical picture. An intradermal skin reaction with histoplasmin, an antigen derived from *Histoplasma capsulatum*, has been developed. Through epidemiological studies with this test it now appears that many of the cases of pulmonary calcification in non-tuberculin reactions may be due to mild or subclinical histoplasmosis. The reliability of the reaction, however, has not yet been fully determined.

**Toxoplasmosis.**—This disease is caused by a protozoan parasite, *Toxoplasma*, of crescentic shape, and measuring 7 microns in length and from 2 to 4 microns in width, although in sections of fixed tissues they may be considerably smaller. The parasite is of wide distribution in animals, occurring in the dog, mouse, rat, rabbit, etc. Very few human cases have been reported, mostly in infants. Infection is probably acquired by man from infected animals. In infants transmission appears to be from the mother, although she shows no evidence of the disease.

In infants the chief lesion is an encephalitis. Microscopically small necrotic and granulomatous lesions are found, the nerve cells being crowded with the parasites. In adults the lungs show foci of consolidation, the cells lining the alveoli being swollen and filled with parasites, whilst the alveolar spaces are occupied by an exudate of mononuclear cells. The blood contains neutralizing antibodies. The infection can be transmitted from the human lesions to experimental animals.

## • WORMS OR HELMINTHS

The parasitic worms may be divided into flat worms and round worms. The flat worms are subdivided into flukes and tapeworms. Only the more important of the disease-producing worms will be considered.

**Flukes.**—The flukes are small, flat, leaf-shaped, unsegmented worms. Liver flukes are common parasites of sheep and cattle, living in the bile ducts and producing inflammation of the liver. Infestation of the liver in man is very prevalent in China, where it is caused by *Clonorchis sinensis* (Chinese liver fluke) (Fig. 87). *Fasciola hepatica* (sheep liver fluke) is met with in sheep-raising countries. The lung fluke (*Distomum pulmonis*) is a common parasite in China and Japan where it is an important cause of hemoptysis; the ova are found in the blood-stained sputum.

**Bilharzia *Hæmatobia*.**—This, also known as *Distomum hæmatobium* and *Schistosoma hæmatobium*, is the most important of the flukes. It causes widespread disease in Egypt and other parts of Africa. The population of Egypt is 12,000,000; 6,000,000 of these are infected, and 1,000,000 are bed-ridden owing to the disease. The adult worms, only 1 cm. long, live in the hepatic veins where they do no harm. The mature female migrates to the pelvic veins and the eggs are laid in the wall of the bladder and the rectum. The ova are provided with a sharp spine which causes great irritation of the mucosa of the bladder and rectum. Chronic cystitis and hematuria result. Polypoid masses are formed in the bladder, and these may become the starting-point of carcinoma. The ova are discharged in the urine and can be readily recognized by the characteristic spine. Pulmonary lesions are found in some 33 per cent of cases (Shaw and Gharceb). The ova become impacted in the pulmonary arterioles, causing an acute necrotizing arterio-

litis, as a result of which the ova escape into the lung and produce a parenchymatous tubercle. In the great majority of cases only a few ova reach the lungs, and only a few tubercles are formed. When the infestation is heavy there may be an obliterative arteriolitis, which in rare cases gives a clinical picture of Ayerza's disease with death from congestive heart failure. A water snail appears to be the intermediate host, and the active embryos which escape from the snail can penetrate the skin of persons while bathing.

**Cestodes or Tapeworms.**—There are four tapeworms of importance in human pathology.

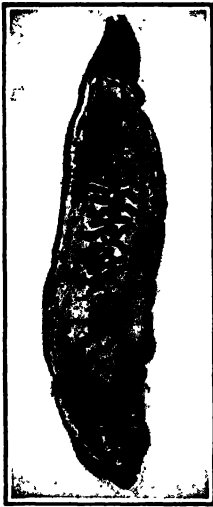


FIG. 87.—*Clonorchis sinensis*.

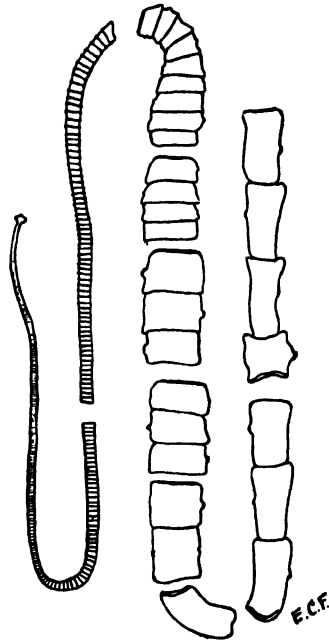


FIG. 88.—Strobila of *Tænia saginata*. Two-thirds natural size. (After Leuckart, *Parasiten des Menschen*.)

Three of these pass an adult stage in the intestine of man and a cystic stage in an intermediate host. They are known as the beef tapeworm (*Tænia saginata*), the pork tapeworm (*Tænia solium*), and the fish tapeworm (*Diphyllobothrium latum*). The fourth (*Tænia echinococcus*) passes the cystic stage in man (the intermediate host) and the adult stage in the dog; this is the one which causes hydatid disease, and is the only really dangerous member of the group.

***Tænia Saginata* (*Tænia Mediocanellata*).**—The beef tapeworm is the common tapeworm of the United States and Canada. It is the largest tapeworm and it has the largest intermediate host. It consists of a tiny head or scolex and segments or proglottides. (Fig. 88.) The head is 2 mm. in diameter and possesses four suckers by which it

adheres to the intestinal mucosa. It has no hooks. The worm may be 30 feet long and possess some 2000 proglottides. The proglottides are crowded with eggs, and as these become mature the segments break off and are discharged in the feces. When taken up by cattle the ova develop into embryos which migrate to the muscles and there develop into cysticerci. If the beef from an infected cow is eaten imperfectly cooked or in a raw state human infection will result. The diagnosis is made by finding the segments in the feces. The worm, which is usually single, causes wonderfully little disturbance in spite of its great length.

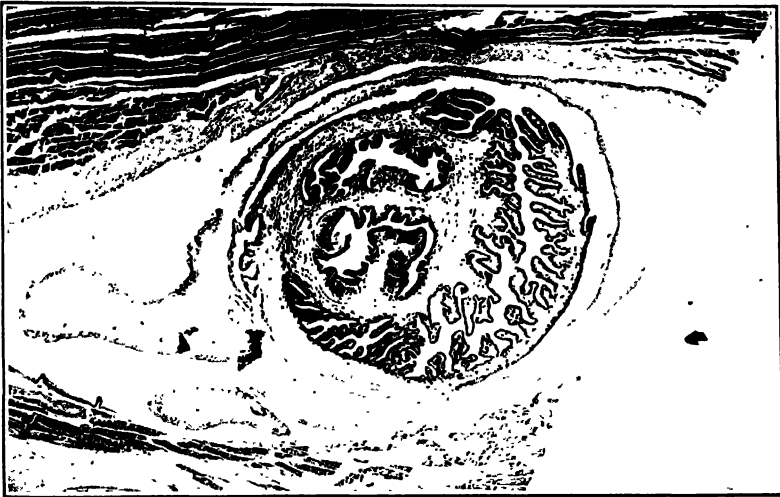


FIG. 89.—*Cysticercus cellulosæ* showing continuity of epithelium on surface and that lining body canal.  $\times 22$ .

**Tænia Solium.**—The pork tapeworm is much rarer than *Tænia saginata*. It is usually under 10 feet in length and resembles *Tænia saginata*. The head, however, is armed with a double row of hooks. Generally only one worm is found (*solium* means single), but in a few instances there may be two or three. The pig is the intermediate host, its muscles contain large numbers of *cysticercus cellulosæ*, and man is infected by eating imperfectly cooked "measly" pork. The eggs may be swallowed owing to self-infection and occasionally the embryos invade the body and develop into the larval cystic form, man thus acting as the intermediate host. This does not occur with *Tænia saginata*. The *cysticercus cellulosæ* thus formed may be present in large numbers in the brain, meninges, eye, muscles, and other organs. The larval worm is inverted and the epithelium of the highly tortuous canal of the body becomes continuous with epidermis covering the outside of the cyst. (Fig. 89.) MacArthur has shown that many soldiers who develop idiopathic epilepsy some years after serving in

the tropics are really sufferers from cerebral cysticercosis. In the Millbank Military Hospital in London there were 20 cases in one year. The parasites may be present for years before symptoms develop, for they are tolerated while alive, but act as foreign irritants when they die. They become calcified, and can be seen in radiographs of the muscles. As a rule there is no history of intestinal infection in these cases of cerebral cysticercosis cellulosa.

**Diphyllbothrium Latum (Bothriocephalus Latus).**—The fish tapeworm has from 3000 to 4000 segments filled with eggs. The eggs are discharged from the ripe proglottides, but only empty and shrivelled segments are shed, in this respect differing from the other two tapeworms. It follows that in stool examinations the presence of ripe segments indicates *Tænia saginata* or *Tænia solium*, the presence of eggs indicates *Diphyllbothrium latum*. The average output of eggs in the stool per day is 1,000,000. The tiny head is flattened and does not possess suckers or hooks but is provided with two longitudinal suckorial grooves. When the ova are discharged they develop into free-swimming larvæ and these are taken up by small water crustaceæ which are in turn devoured by some of the larger fish (pike, perch, etc.), where they invade the muscles and pass into the cysticercus stage.

The geographical distribution is important. It used to be found principally among the fish-eating peoples in the Scandinavian countries, Russia, and in parts of Asia, but lately it has been imported into the United States and Canada, and is now indigenous in the districts around the Great Lakes and Lake Winnipeg. The fish in these lakes are probably infected from dogs, who also harbor the parasite. If the fish are properly cooked there is no danger.

A large number of the worms may be found in one person. In 999 out of 1000 infected persons it is a harmless parasite, provided that the patient is unaware of its presence, although a mild hemolytic anemia is common. In very exceptional cases the patient may develop a severe anemia identical in type with pernicious anemia, but this is seldom seen even in fish-eating communities where the infection is extremely prevalent; only in Finland is the anemia at all common.

**Tænia Echinococcus.**—This tapeworm is entirely different from the others. It is extremely small, measuring only 5 mm. in length, and possesses only 3 proglottides. The cystic stage is passed in man and many other animals and the adult stage in the intestine of the dog, where there may be hundreds of worms. Man therefore serves as the intermediate host. Human infection is usually due to eating unboiled vegetables soiled by the excreta of dogs. The dogs are infected by eating the flesh of infected sheep. Hydatid disease, as the human infection is termed, is most prevalent in Australia, South America, and other great sheep-raising countries, where dogs and men come into very close contact. Syria has perhaps the largest incidence. Iceland used to be a hot-bed of the disease, but during recent years it has been nearly eradicated by hygienic measures.

When the eggs are swallowed by man they develop into embryos

which penetrate the wall of the bowel and are carried in the portal vein to the liver and through the liver to any other part of the body. The embryos form larval cysts (hydatid cysts) which are naturally most common in the liver and mesentery. The cyst consists of two layers. The outer layer or ectocyst is white and presents a characteristic laminated structure like the coats of an onion. The inner or germinal layer is granular and it is in this material that fluid collects so that a cyst is formed. At various points along the germinal layer buds arise which become hollowed to form brood capsules in which little clusters of new scolices on stalks are produced. (Fig. 90.) Some of the buds develop into daughter cysts which become detached and float in the cavity of the mother cyst. From the lining of the daughter cyst new buds may arise which in turn produce new scolices. Each

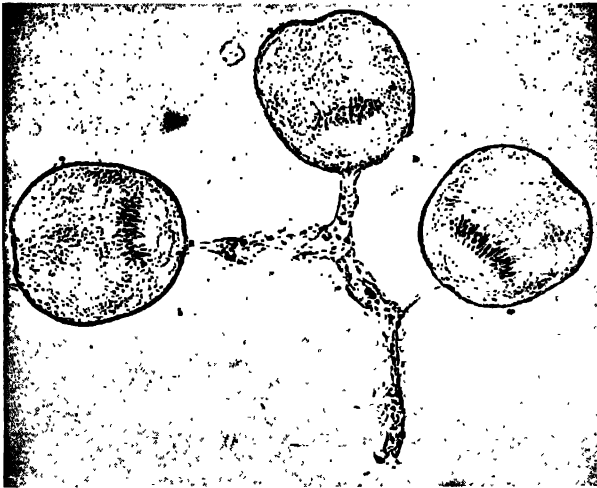


FIG. 90.—Stalked scolices of hydatid cyst showing hooklets.  $\times 200$ .

scolex is provided with 4 suckers and a crown of 30 to 50 hooklets. The scolex becomes invaginated into its own body in order to preserve the hooklets from injury, so that the suckers and hooklets face inward. (Fig. 91.) When the infected material (in the sheep or other intermediate host) is eaten by a dog the head is evaginated, and the scolices become attached to the intestinal wall by their hooklets and suckers, proceed to form proglottides, and develop into the mature worm.

The cysts may attain a great size and cause marked enlargement of the liver, form masses in the mesentery, etc. The fluid is clear and sterile, but contains a toxic substance which may cause attacks of urticaria or produce toxic effects if the cysts are ruptured during removal. The blood may give a complement-fixation reaction against this substance. Intradermal injection of the fluid is said to give a specific reaction in cases of hydatid disease. Identification of the cysts

is made by finding the characteristic hooklets, or by cutting sections of the wall and demonstrating the laminated structure of the ectocyst. (Fig. 92.)

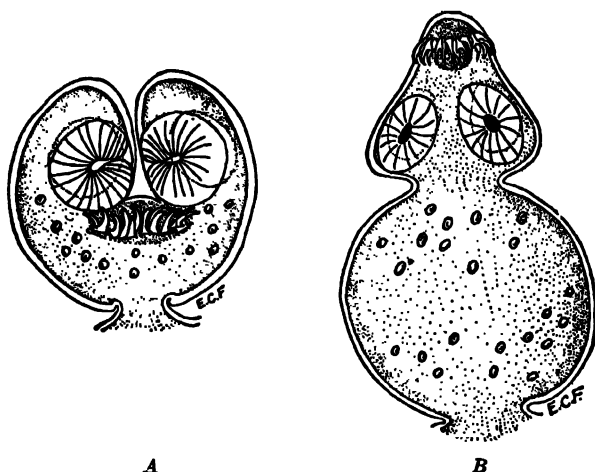


FIG. 91.—Scolex of hydatid cyst. *A*, Invaginated in cyst membrane; *B*, with evaginated hooklets and suckers.  $\times 400$ . (Faust.)

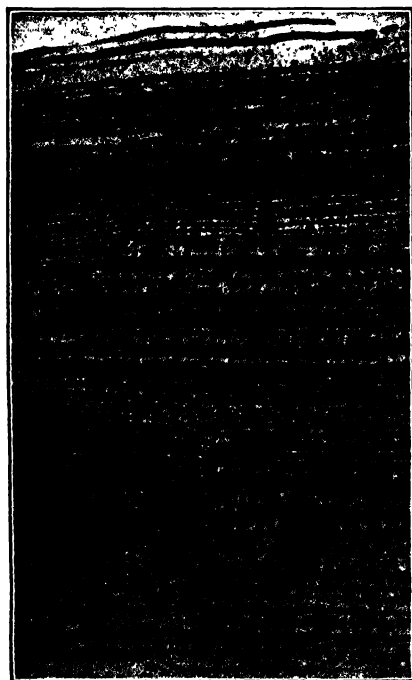


FIG. 92.—Laminated membrane of hydatid cyst.  $\times 200$ .

**Echinococcus Alveolaris.**—There are two forms of echinococcus: *E. hydatidosus*, which has just been described, and *E. alveolaris* or *multilocularis*, a much rarer form. The hydatid echinococcus forms large cysts filled with fluid, but the alveolar echinococcus cysts are entirely different, being extremely numerous, varying in size from the microscopic to that of a grain of seed or a pea, and containing gelatinous material but as a rule no scolices. They cause great enlargement of the liver, which at autopsy may be mistaken for mucoid carcinoma or congenital cystic liver. Necrosis may develop, with the formation of large ragged abscess cavities. The microscopic appearance may closely simulate tuberculosis with necrosis, epithelioid cells and giant cells. The disease is fairly common in Bavaria, Switzerland, and Russia, but is practically unknown in the great hydatid countries such as Australia, South America, and Iceland.

**Nematodes or Round Worms.**  
—A large variety of round worms



may be parasitic for man both in tropical and temperate countries. Some of these are pathogenic, others are not. Only six will be considered here.

**Ankylostoma Duodenale (Uncinaria Duodenalis).**—Ankylostomiasis or hookworm disease, like malaria, is one of the most prevalent diseases in the world. The Rockefeller Commission estimated that there were some 900,000,000 cases. The hookworm belt extends round the world on either side of the equator. The American variety of the worm is slightly different and is called *Necator americanus*. It is also found in temperate climates where the conditions are such that the soil is moist and warm as in deep mines, in long tunnels, etc., so that hookworm disease is known locally as miners' anemia, tunnel disease, etc., and the skin manifestations are known as ground itch. The reason for all this will be apparent shortly.

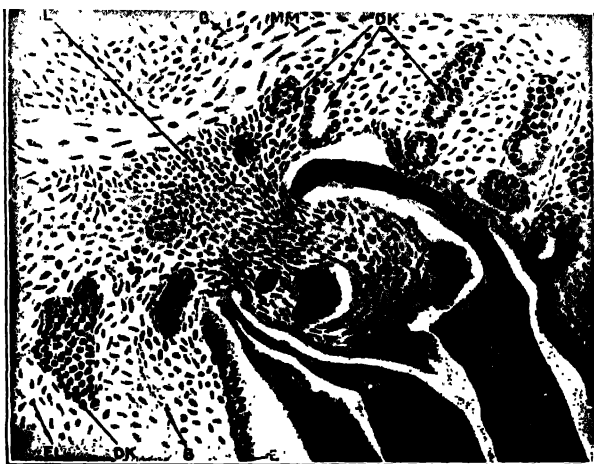


FIG. 93.—Section through human intestine, showing method of attachment of hookworm to the wall. (After Oudendal, in Transactions of Fifth Biennial Congress of Far Eastern Association, Courtesy of John Bale Sons & Danielsson, Ltd., London.)

The worm, as its name implies, lives in the upper part of the small intestine, although more in the jejunum than the duodenum. Large numbers, even hundreds, are found hanging firmly attached to the intestinal mucous membrane. It is said that as many as 10,000 have been found in one person. The worm is quite small, from 1 to 2 cm. in length, and is furnished with four teeth (*ankylos*, hooked), and a muscular esophagus by means of which the intestinal mucosa is drawn into the mouth. (Fig. 93.) The patient develops a profound anemia as the result of this heavy infection. This is due to the peculiar feeding habits of the hookworm, which draws blood from the mucosa of the bowel, pumps it through the alimentary tract, and forces it out from the anal orifice, a process which can be watched in the experimental animal. By means of such a mechanism 10,000 worms can soon

remove a lot of blood. There is marked eosinophilia, a common manifestation of worm infections. The patient becomes weak, apathetic, and unable to work. There is marked evidence of anemia, including edema of the face.

The *mode of infection* provides one of those romances which makes the study of parasitology so interesting. The worms may live for six or seven years in the bowel, but they cannot multiply there. The eggs, of which 10,000,000 may be laid at one time, are passed in the feces, and if deposited in warm moist soil they develop into active embryos. These may be swallowed by another person, but the usual route is quite different and much more remarkable. In 1901 Looss, working in Egypt, showed that the hookworm sets forth on a veritable Odyssey in its effort to reach the small intestine. If wet mud containing the larvæ is rubbed on the skin a burning and itching is soon



FIG. 94.—Hookworm larva (coiled) penetrating the skin. (Stumberg, Am. J. Hygiene.)



FIG. 95.—Hookworm dermatitis. (Dove, Am. J. Hygiene.)

experienced, and by the time the mud is dry the active larvæ have disappeared through the skin leaving their own skins behind them. Looss followed their course in a leg about to be amputated. The larvæ are found to penetrate the hair follicle (Fig. 94), and from there they bore their way into the lymphatics by which they are carried to the venous blood stream or they may penetrate the veins directly. They are carried by the venous blood to the right heart and thence *via* the pulmonary artery to the lungs. When large numbers of larvæ enter the lungs it is common to find bronchitis and transient bronchopneumonia. In experiments on dogs it was found that the larvæ are filtered out of the circulation in the lungs, being unable to pass through the pulmonary capillaries. They burrow into the air vesicles, enter the bronchi, and crawl up the trachea. Having reached the glottis they climb over the epiglottis and down the esophagus. The further passage through the stomach and into the duodenum is plain sailing. In the small intestine they develop into adult worms. How long the

larvæ takes to complete their Odyssey it is difficult to say, but as long as ten weeks has elapsed between the skin infection and the appearance of the eggs in the feces.

Ashford has added an important chapter to the story of the hookworm cycle by describing what he calls the larval stage of uncinariasis. He points out that the majority of the larvæ which penetrate the skin never reach the intestine, but die soon after invasion, as shown by the fact that the highest leucocytosis and eosinophilia occur at the beginning of the infection. Many other larvæ stray from the direct path and get hopelessly lost, remaining wanderers in the tissues until they perish. At the end of three months there is a second rise in the leucocyte count, due to the end of the natural term of life of the larvæ. During the larval stage there may be no adult worms in the bowel, but the patient suffers from marked lassitude, while his blood shows an eosinophilia. The latter, which may reach 60 per cent, appears to be due to disintegration of the larvæ and absorption of the foreign protein. Ashford's paper will be found extraordinarily interesting reading.

It is evident that coolies in coffee plantations, natives working in the mud on the banks of the Nile, miners in deep mines, tunnel-workers, etc., are peculiarly liable to the disease once the ground is heavily infected. The "ground itch," an eczematous skin eruption which affects those who walk in infected water with bare feet (Fig. 95) is merely an indication that the larvæ are invading the skin. When native workmen in hookworm areas are compelled to wear shoes the incidence of the disease shows a marked falling off. Proper disposal of excreta is another factor of prime importance in prevention of the disease. The diagnosis is made from the anemia, the eosinophilia and the presence of ova in the stools.

**Ascaris Lumbricoides.**—This is the common round worm which resembles the earthworm, being from 6 to 16 inches long, with tapering pointed end and a pearly-white appearance. It is a common inhabitant of the small intestine, especially in children in whom it may produce reflex nervous disturbances; possibly a toxic element may also play a part. The worms, of which there are usually several, appear in the mouth. They lie free in the lumen of the bowel, and are not attached to the wall. Occasionally they are present in enormous numbers and may form masses which cause intestinal obstruction.

Although the ascaris is so different from the hookworm, yet parts of their life history are not dissimilar. Indeed, the behavior of the ascaris is even more strange. The ova develop into embryos in moist soil. The freshly passed eggs are not infective, and ten days or more must elapse before they are capable of causing infection. The capacity of the uterus has been estimated at about 27,000,000 eggs, and the average daily output for each female at 200,000. Infection is due to the ingestion of developing eggs on uncooked vegetables, etc. When the eggs are ingested they hatch into larvæ in the intestine. But here we come to the strange part. The larvæ are apparently unable to

undergo complete development in the intestine until they have undertaken an extra-intestinal migration. They penetrate the wall of the intestine and are carried to the right side of the heart either by the lymph and blood stream or by the mesenteric veins and inferior vena cava. They are filtered out by the lungs, and pass up the trachea and down the esophagus into the intestine just as in the case of the hookworm. This strange migration occupies about ten days. In the intestine they develop into maturity if they have been derived from a human source, but not from the pig. In the latter case they are passed out of the body.

In the pig, on which animal most of the experimental observations have been made, large numbers of larvæ can be seen in sections of the lungs, as well as foci of hemorrhage and inflammation. In man the experimental ingestion of mature eggs has been followed in a few days by the development of the clinical picture of pneumonia. Koins swallowed approximately 2000 eggs; six days later he developed fever, chills, headache, malaise, rapid respirations, and a productive cough with the blood and larvæ (178 in one day) in the sputum. There was dulness over the chest and crackling râles. In clinical practice only a few eggs are likely to be taken at any one time, so that as a rule there are no physical signs. Ashford suggests that, as in ankylostomiasis, the larvæ may become lost and wander through the tissues, and that the presence of larvæ in the meninges may be responsible for the convulsions and nervous disorders in young children.

**Oxyuris Vermicularis (Enterobius Vermicularis).**—The thread worm or pin worm is a very common intestinal parasite, especially in children. It is only about 5 mm. long, and when passed in the stools resembles a motile piece of white thread. It lives in the lower part of the small intestine and the large intestine. The worms may pass out *per anum* and cause intense irritation and itching around the anus and in the vagina. A simple diagnostic method is to make a smear from the perianal region and examine it for ova, which adhere to the hairs in large numbers. In the bowel they usually cause no symptoms, but in weakly children they excite reflex nervous disturbances such as convulsions and enuresis. Masses of thread worms may occupy the lumen of the appendix. They may invade the mucosa and cause acute appendicitis. There is no intermediate host, and infection is direct from contaminated vegetables, fruit, etc. Massive reinfection may occur from the child's contaminated fingers.

**Trichina Spiralis (Trichinella Spiralis).**—The disease trichiniasis is caused by a tiny round worm, the life history of which presents some very interesting features. It passes its complete life cycle in the body of one animal, but unless the host be eaten by another animal the embryos will all die. Surely a curious arrangement to have been evolved by a worm, but apparently a satisfactory one.

The parasite infects a variety of animals, in particular the rat, the pig, and man. Man becomes infected by eating the pig, and the pig is infected by eating the rat. Thus the life cycle is continued, but it

comes to an end with man. Epidemics occur, particularly in Germany, from eating imperfectly cooked pork in sausages, etc. The embryos ingested in the infected pork develop into adult male and female worms, in the intestine. These are very tiny, from 1 to 3 mm. long. After copulation the males die and the females burrow into the intestinal villi. The ova develop into embryos within the uterus of the worm, and the embryos are then discharged into the lymphatics. One female may discharge from 1000 to 1500 embryos in this way. The embryos enter the blood stream, and as their diameter is smaller than that of a red blood cell (6 microns broad though 100 microns long), they pass through the lungs and are carried to all parts of the body. During the stage of invasion they can be found in the blood if it is laked and in the cerebrospinal fluid. They are actively motile, and penetrate the capillaries to invade the various organs. But they can only develop in the voluntary muscles and die out elsewhere, even in the heart. Every muscle in the body may be infected and yet the heart always escapes. Even it is probably infected at the beginning as indicated by the frequent presence of inflammatory foci, but the young embryos are apparently killed and disappear at an early stage.

Each embryo now enters a muscle fiber and undergoes partial development toward an adult worm, but full development is not possible unless the parasite finds itself in the digestive canal of another animal. The muscle fiber degenerates and loses its transverse striations. The embryos are found in the muscles as early as the ninth day after infection. They set up an acute myositis with infiltration of polymorphonuclears, eosinophils, lymphocytes, and giant cells. At first the long axis of the embryo is parallel to that of the muscle fiber, but by the end of the second week it becomes coiled up, encysted, and surrounds itself with a thick hyaline capsule. (Fig. 96.) Later this may become calcified. The encysted embryos are lemon-shaped, with the long axis in the direction of the muscle fibers. The embryos may remain alive for years awaiting the chance to complete their development in another animal. The life cycle is exactly the same in the pig. When the encysted embryos are swallowed by man the capsule is dissolved by the digestive juices, the embryos are liberated, and may attain maturity in a couple of days, when the whole process is repeated.

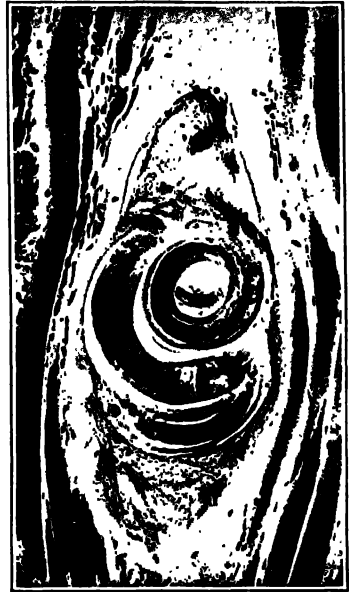


FIG. 96.—*Trichina spiralis* in muscle.  $\times 175$ .

**Symptoms.**—The symptoms of trichiniasis occur during the period of invasion and are partly due to the irritation in the intestine, partly to the acute myositis. The muscles are hard and swollen and often extremely painful. Edema is usually present and is often marked in the face. Fever is a common symptom and may last for days or weeks. The severe cases are easily mistaken for typhoid fever, especially when there is diarrhea, but the leucocytes are increased in number and there is a marked and very characteristic eosinophilia, sometimes over 50 per cent. The eosinophilia usually disappears, but may persist for years. Convalescence sets in about the sixth week, but death may occur earlier from paralysis of the respiratory muscles. Many cases die in the early stage of the infection, apparently from the intense irritation in the wall of the intestine. The intradermal injection of a saline extract of trichina larvæ gives a positive reaction in about 90 per cent of cases after several weeks of infection. A positive reaction may still be obtained several years after the acute attack.

**Filaria.**—Filariasis is an infection by a nematode worm in which the adult worm lives in the lymphatics while the larvæ travel in the blood. It is a disease of tropical countries. There are several varieties of filaria, the most important being *Filaria bancrofti*, the larval or microfilarial form of which is known as *Filaria sanguinis hominis*. This parasite is of great historical interest, because it was in connection with it that Manson showed for the first time the part which the mosquito plays in the transmission of disease. It was Manson's work which suggested to Ross that malaria might also be conveyed by a mosquito, even though the infecting agents were so very different—the one a nematode worm, the other a protozoan parasite.

The life history and habits of the filaria are remarkable even for an animal parasite. The adult worm lives in the lymphatics, especially those of the groin and pelvis. It is from 0.5 to 1 cm. in length and extremely thin. The male and female live together, and the ova develop in the uterus of the female into active larvæ. These are little eel-like bodies with a diameter no greater than that of a red blood corpuscle, so that they can pass through the smallest capillaries. Their most extraordinary characteristic is their periodicity, for they only appear in the peripheral circulation at night, hiding in the vessels of the lung and the large thoracic vessels during the day. Their appearance synchronizes with the evening appearance of the mosquitoes, for they can only attain maturity in the body of that insect. One wonders how such an arrangement was first started. If the patient sleeps during the day and is kept awake during the night the larvæ are deceived and come out by day, so that the mosquitoes are disappointed. The larvæ do the patient no harm. This nocturnal periodicity may go on for years, the larvæ patiently awaiting the coming of the mosquito.

Lane points out that the usual explanation of filarial periodicity is not to be lightly accepted, for the hiding place of the larvæ by day has never been demonstrated, and it seems unlikely that they can maintain themselves in position in the large vessels of the thorax

against the strong current of blood. He suggests that there may be a daily cyclical parturition by the females, and that the microfilariae perish rapidly. This view is supported by the observations of O'Connor who made serial sections of lymphatic tissue containing worms excised at operation. One extraordinary fact was brought to light. When the worms were removed before mid-day the turgid female was found to be crammed with microfilariae, but after 2 P.M. the females were collapsed and empty. All the living female worms from the same patient showed the same stage of development of the sex cycle. In a volunteer 720,000 microfilariae were injected into the blood stream; all were gone in the space of two hours. Destruction apparently takes place chiefly in the lymph nodes.



FIG. 97.—Extreme degree of elephantiasis of scrotum in African negroes.

The *mosquito*, usually a member of the genus *Culex*, bites an infected person, and the larvæ pass with the blood into its stomach. They penetrate the stomach wall and lodge in the thoracic muscles. Here they develop into young worms which make their way to the base of the proboscis and await injection into man, where sexual development may be attained and reproduction take place. The parasite is not actually injected by the mosquito but is deposited close to the hole in the skin made by the proboscis, and through this hole it penetrates the skin. It is said that the worms often pass out in pairs—probably male and female. They pass to the lymphatics, become mature, larvæ are liberated into the blood, and the cycle is complete.

*Pathological Effects.*—There may be none, though the patient may have larvæ in his blood for years. The adult worms are apt to produce *lymphatic obstruction*, especially if they are present in masses, and above all if they die and disintegrate. The obstruction causes varicosity of the superficial vessels and lymphatic edema. The regional lymph nodes are enlarged, their sinuses being distended with lymph. *Ele-*

*phantiasis* may develop. This is a condition in which the tissues become enormously thickened and indurated. The legs and scrotum are the parts commonly affected. (Fig. 97.) It is probable that lymphatic obstruction alone will not give rise to elephantiasis, but that infection and lymphangitis must be superadded. The abdominal lymphatics may rupture, especially if there is obstruction of the thoracic duct, and lymph escapes into the peritoneal cavity giving *chylous ascites*. If the renal or vesical lymphatics are obstructed there may be *chyluria*. The patient may show small subcutaneous nodules not necessarily associated with edema. These represent an inflammatory reaction around a coiled-up worm. I have seen such a nodule removed from the arm under the impression that it was a thrombosed vein. (Fig. 98.)



FIG. 98.—*Filaria* in a small vessel.  $\times 40$ .



FIG. 99.—*Dracunculus* worm partially removed from a ruptured eschar of the fourth toe. (After Castellani and Chalmers, Tropical Medicine.)

***Dracunculus Medinensis* (*Filaria Medinensis*, Guinea-worm).**—This parasite of tropical countries, commonly known as the guinea-worm, is surpassed by none of its relations in peculiarity of behavior. As usual the male is insignificant, but the female is long and very thin; the average length is 50 to 80 cm., but it may reach  $1\frac{1}{2}$  meters. The intestinal canal is atrophic and the anus absent, but the uterus, crowded with larvæ, runs almost the entire length of the worm. The larvæ have to be discharged into water, and the female finds the necessary water with a certainty which a water-diviner might envy. The worm works its way through the tissues until it reaches a surface.



As the natives go bare-footed, the worm usually makes its appearance on the sole of the foot, but it appears in upper extremities of Europeans, where water is more often in contact with the hands and arms, and on the backs of water-carriers whose water-skin is slung over that part. The passage down the leg may take as much as eighteen months. The head of the worm pierces the surface with the formation of a small blister, and when water is poured on the skin enormous numbers of larvæ are discharged from the greatly distended uterus so that the fluid becomes milky. The larvæ are taken up by a fresh-water crustacean belonging to the genus *Cyclops*, in which they pass through a necessary stage of development before being ingested by man. It is for this reason that the worm has to make for water, however long the journey may be.

If the worm dies or if the larvæ are liberated into the tissues as the result of injudicious attempts at removal, there may be severe inflammation and abscess formation. The natives have an ingenious method of persuading the worm to leave its habitat. They pour water on the foot, and in the resulting effort of parturition the worm is induced to emerge on the surface. The protruding part is wound round a small stick and the treatment is repeated at intervals, the stick being given an additional twist on each occasion. By this simple means as the result of patience and perseverance the worm can finally be completely removed. (Fig. 99.) It has been suggested that these worms were the "fiery serpents" which afflicted the Children of Israel in the migration from Egypt, and that Moses was the first in history to demonstrate the classical method of removal by winding the "serpent" on a rod gradually drawing it out. He made a model in brass of the procedure.

### EXTERNAL PARASITES. ARTHROPODS

Some of the more common of these will be merely mentioned. For detailed description the reader is referred to works on skin diseases and parasitology. A few of the external parasites are of importance not only because of the irritation they produce but because of the much more serious diseases which they may be the means of carrying. The commonest skin parasites are "itch insect" causing scabies, lice and fleas.

**Acarus Scabiei.**—The "itch insect" which causes scabies is shaped like a turtle and about 0.5 mm. long. (Fig. 100.) The impregnated female bores a tunnel into the skin, laying her eggs at the end of the tunnel where the young are hatched. These in turn bore new tunnels. The male remains quietly on the surface and causes no trouble. The symptoms of scabies depend on the irritation produced by the burrowing female. The burrows take the form of curved dark lines, and are most common between the fingers, at the wrists, in the axillæ, etc. Vesicles may form at the entrance to the burrows and these are often infected by the scratching induced by the intense itching.

**Pediculi.**—A variety of pediculi or lice may infest the body. *Pediculus capitis*, the head louse, lies on the scalp. (Fig. 101.) The ova or "nits" are minute white bodies which can be seen attached to the hairs. They hatch out in about a week. *P. corporis*, the body louse, lives on the surface of the skin and breeds in the clothing. By its bites it causes great irritation of the skin, and the itching causes scratching with subsequent infection. The body louse is responsible for carrying the infection of typhus fever, relapsing fever, and trench fever. It does this in the same way as the mosquito, *i. e.*, by biting

first a sick man and then a healthy person. *P. pubis* is found especially in the pubic region.

**Fleas.**—*Pulex irritans* is the common flea, a wingless insect 2 to 4 mm. long. *P. cheopis*, the rat flea, is of importance because it conveys plague not only from one rat to another but also from rat to man.

**Flies.**—The body tissues or cavities may be infested with the larvæ (maggots) of certain flies, a condition known as *myiasis*. The eggs may be laid in the nasal cavities, wounds, etc., where they develop into maggots. One type

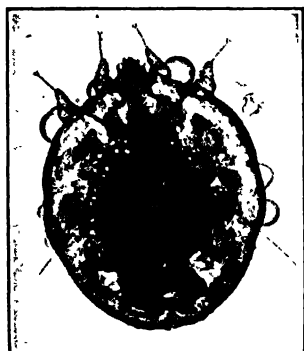


FIG. 100.—*Acarus scabiei*.  $\times 75$ .



FIG. 101.—*Pediculus capitis*.  $\times 30$ .

of larva tunnels about in the skin, causing the condition called "creeping eruption." This condition may, however, be produced in other ways. In the Southern United States probably the commonest cause is the larva of *Ancylostoma braziliense*.

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## CHAPTER IX

### GROWTH AND ITS DISORDERS

GROWTH is the most fundamental of all physiological functions. It is brought about by multiplication of cells, not by increase in their size. There is little difference in size between the cells of a mouse and the cells of an elephant; the difference is one of number. In the same way the cells of a cancer may be actually smaller than those of the tissue from which it arises. The cells of any given species of animal have a strictly limited power of multiplication. When this limit is reached the growth of the animal ceases. This it is which determines the size of animals, so that all members of one species are of approximately the same size, no matter how the external conditions may vary. To this rule the fishes offer an exception, for the members of a species, such as trout, may greatly increase in size when placed in a more suitable environment. Growth is brought about by the change of non-living into living material. All dead matter is potentially living, and we see the transformation of dead into living matter going on ceaselessly. "The molecules of the dead world are waiting to be delivered from the bonds of death," as Lorrain Smith remarks in a delightful monograph which should be consulted by anyone interested in the subject of growth. He points out that theoretically the whole inorganic substance of the material world might be converted into living substance by the substance already living.

Cells not only grow (multiply); they also differentiate. Now differentiation and growth are mutually antagonistic, and this is a profound biological principle. Differentiation depends on environment. Unless cells are compelled by their environment to differentiate they will feed, grow and multiply forever without doing any physiological work, thus resembling human beings. Division and function are not possible at the same time. The more highly differentiated a cell becomes, the more does it lose its power of reproduction, and therefore its ability to give rise to tumor formation; this is seen in the case of striated muscle, nerve cells, red blood cells, etc. Cancer cells fail to differentiate; instead they continue to grow. As Lorrain Smith says, they do not fall into the normal procession. They fall out. They do not keep step; the procession is moving slowly and they move fast. Under normal conditions the cells of the basal layer of the epidermis divide into two; one remains as a basal cell, while the other differentiates as a prickle-cell. In basal-cell cancer all the basal cells retain their original character.

**Tissue Culture.**—One of the most remarkable feats in modern biology is the cultivation of the cells of the animal body under artificial con-

ditions, first accomplished by Harrison in 1907. The cells of a dead body may be made to live, multiply and grow indefinitely. The conditions for the study of growth may be greatly simplified by this method, but it must be realized that this simplification is highly artificial, and the conditions are entirely different from those which govern growth when the cells are in their natural environment. A malignant tumor of connective tissue may be indistinguishable from normal connective tissue in artificial culture, for both will grow indefinitely, but if they are planted again in the body the difference at once becomes apparent. The influence of environment is all-important. At the same time the method of simplification, itself a *tour de force*, has yielded interesting and valuable information.

In tissue culture we find a perfect dissociation of growth from differentiation. There is no work to be done, so the cells merely proliferate. One startling result is that in the case of at least one tissue the mortal cell has "put on immortality." As long as fresh food is provided it can grow and multiply forever. In 1911 a culture of fibroblasts from the embryonic heart of a chick was commenced at the Rockefeller Institute, and it is still growing at the same rate at which it started. This tissue has long outdistanced the possible span of life of the animal from which it was taken; it does not grow old, as those that are left grow old. It would appear, therefore, that senescence is dependent on environment rather than on the cell itself.

In spite of the fundamental difference between growth in the body and growth *in vitro*, some of the basic properties of cells can be studied by this method, as in the work of Carrel and others on the fibroblast and the macrophage. Carrel found that fibroblasts never grow as isolated units, but maintain intimate contact with one another so as to form dense tissue. Indeed they will not proliferate if separated from their neighbors. Macrophages, on the other hand, live as independent units, and die if they congregate in dense masses. By the method of tissue culture Carrel and Ebeling showed that the monocytes of the blood and the macrophages of the tissue are merely functional variations of a single type. When both are cultivated they assume an identical appearance. Macrophages can feed on blood serum, but die in pure embryonic juice. Fibroblasts, on the other hand, thrive in embryonic juice, but stop multiplying in blood serum unless supplied with growth-stimulating substances. These substances, called by Carrel *trephones*, are present in embryonic juice, and also in spleen, leucocytes, and inflammatory tissue. When cultures of fibroblasts and splenic tissue are made a short distance apart in medium containing no embryonic juice, the fibroblasts fail to grow until the lymphocytes from the spleen reach them; then they grow readily. As might be expected, embryonic tissue grows readily in artificial culture, but adult tissue only with difficulty. Tissues vary greatly in their power of growth in culture. The fibroblast grows most readily, and is the only cell which shows evidence of immortality. When a culture is made of embryonic heart it is the fibroblasts which grow, the muscle cells die.

In this way a pure culture can be obtained. Cultivation of the cells of the blood gives a pure culture of monocytes. Epithelium grows well for a time, but after some months it degenerates and dies. The power of embryonic tissue to grow in artificial culture is sometimes remarkable. Strangeways, Niven and others have actually succeeded in making a long bone such as the femur or tibia from a chick embryo grow in length, develop epiphyses, and undergo osteogenesis.

The influence of environment even *in vitro* is well illustrated by the work of Drew. Pure cultures of a tissue such as renal epithelium or renal connective tissue were obtained by placing a minute globule of mercury over a separate clump of the desired cells, subjecting the culture to the lethal effect of ultra-violet light, and then cultivating the tissue protected by the mercury. The renal epithelium grew in an undifferentiated sheet until the correct amount of connective-tissue cells was added, when definite kidney tubules were formed. By providing the necessary stroma heart muscle cells could be made to pulsate *in vitro*, and the mammary epithelium from a pregnant animal to produce fat droplets which made the medium milky. It is evident from such experiments that a tissue culture is in a sense a "partial organism," in which the different parts are in some way coördinated. It has not been possible to grow single cells. The only isolated cell which is capable of independent growth is the ovum. Even *in vitro* the cells are members one of another. It is possible that an exception should be made in the case of the cells of a malignant tumor.

### METAPLASIA

Metaplasia is the transformation of one type of tissue into another type. This process has definite limits. An epiblastic tissue can only produce another epiblastic tissue, mesoblast can only produce mesoblast. Metaplasia is best seen in the closely-related connective tissues, as when cartilage is converted into bone. *Anaplasia*, or reversionary atrophy, must not be confused with true metaplasia. Anaplasia is merely the reversion of a more highly to a less highly differentiated form. In fibroid conditions of the lung the flattened respiratory epithelium of the alveoli may revert to the cubical form of epithelium characteristic of the fetal lung; in chronic nephritis the high epithelium of the convoluted tubules changes to a low cubical type.

**Epithelial Metaplasia.**—True metaplasia occurs in response to a call for altered function or at least as the result of altered environment. If the prolapsed uterus becomes everted the columnar epithelium is changed into a squamous stratified form better fitted to withstand friction. As the result of continued irritation, *e. g.*, from gall stones, the columnar epithelium of the gall-bladder may also become squamous, and from this altered epithelium a squamous-cell carcinoma may arise. The bronchial epithelium in a bronchiectatic cavity may undergo the same change and come to resemble the epidermis. (Fig. 102.) The

more highly specialized glandular epithelia (liver, kidney, etc.) appear to be incapable of true metaplasia.

**Connective-tissue Metaplasia.**—Examples of this are of common occurrence. Fibrous tissue, myxomatous tissue, cartilage, and bone are all closely related, and one may become changed into the other. The commonest change is that of cartilage into bone. In old age ossification of the laryngeal and tracheal cartilages is common enough. This is certainly not due to altered function, but may be connected with altered environment. Bone may be formed in the walls of degenerated arteries the seat of arteriosclerosis, or in an eye which is destroyed and functionless. It may be encountered in the edges of a wound in the abdominal wall. Apparently the connective-tissue



FIG. 102. —Remarkable metaplasia of epithelium lining a bronchiectatic cavity. The single layer of columnar cells is converted into typical stratified squamous epithelium.  $\times 150$ .

cells become converted into bone-forming cells. In myositis ossificans bone is formed in the voluntary muscles and may replace them to a large extent; this bone is probably formed from the connective tissue between the muscle fibers. Many examples of metaplasia are seen in connective-tissue tumors; thus the cells of an osteogenic sarcoma of bone may form fibrous tissue, mucoid tissue, cartilage or bone.

**Endothelial Metaplasia.**—When serosal endothelium such as that lining the pleura or peritoneum is irritated either experimentally or by disease it may undergo marked metaplastic changes. In place of being flattened it may become cubical, columnar, or even stratified. The cubical and columnar cells may surround spaces so as to give a glandular appearance. We shall have to return to the subject of

serosal metaplasia in discussing serosal cysts of the appendix and Fallopian tube, endometrial implants of the ovary, and endothelioma of the pleura.

### ATROPHY

Atrophy is a diminution in size, a shrinking of cells or fibers which have reached their full development. Hypoplasia indicates a failure of full development. Atrophy may occur under a great variety of different conditions. Some of the most important of these are old age, lack of nourishment, disuse, the action of toxins, pressure and interference with nerve supply. As *age* advances there is a general tendency towards atrophy, best seen in the uterus, ovary, breast, lymphoid tissue, and bone-marrow. Chronic *starvation* causes wasting of adipose tissue and muscles; atrophy also follows decreased blood supply due to arteriosclerosis. *Disuse* of a structure results in atrophy, as is seen in the anterior horn of the spinal cord after amputation of a limb. *Toxins* are responsible for the wasting seen in long-continued infections. *Pressure* atrophy is seen in the erosion of bone by an aneurism or the atrophy of liver cells in amyloid disease. *Neurotrophic* atrophy is due to loss of trophic impulses when a motor nerve is injured, but it is difficult to be sure how much of this is due to disuse.

### HYPERTROPHY AND HYPERPLASIA

**Hypertrophy.**—Hypertrophy is an increase in the size of individual cells or fibers as a result of which the organ may become enlarged. Enlargement of an organ from any other cause should not be called hypertrophy. There is no increase in the number of the individual elements; such an increase is covered by the term *hyperplasia*. True hypertrophy never occurs as the result of irritation, but always in response to some demand for increased function. It is convenient to recognize three varieties of hypertrophy—physiological, adaptive, and compensatory—although the dividing lines cannot be drawn too sharply.

**Physiological Hypertrophy.**—Physiological hypertrophy occurs apart altogether from disease. The best example is the pregnant uterus. At the end of pregnancy the muscle fibers are ten times as long and four times as broad as in the non-pregnant uterus. The hypertrophy of muscles which follows hard work (the blacksmith's arm) may be placed in this group or in the next.

**Adaptive Hypertrophy.**—Adaptive hypertrophy is best seen in hollow muscular organs when the outlet is partially obstructed. The wall of the organ becomes thickened owing to an increase in the size of the muscle fibers. As examples may be mentioned the left ventricle in stenosis of the aortic valve or high blood-pressure with its increased peripheral resistance (Fig. 104), the stomach in pyloric obstruction, the bowel in chronic intestinal obstruction, and the bladder in stricture of the urethra. The hypertrophy of voluntary muscle as the result of exercise may be placed in this group or in the preceding one.



**Compensatory Hypertrophy.**—Compensatory hypertrophy is an increase in size to compensate for loss of tissue. It is best seen in paired organs. When one kidney is removed or atrophies because of disease the remaining kidney does the work of the two and becomes correspondingly enlarged. (Fig. 103.) There is no formation of new elements, but merely an increase in the size of the existing tubules and glomeruli. When a portion of the liver or thyroid is removed the organ is restored to its original size, a process often spoken of as compensatory hypertrophy, but this is a hyperplasia rather than a hypertrophy.

**Hyperplasia.**—By hyperplasia is meant an increase in the number of the cells of a part. Its limits are more shadowy than those of hypertrophy, and it gradually merges into the process of neoplasia or tumor formation.

Hyperplasia, unlike hypertrophy, is often the result of irritation, although it may also be compensatory or adaptive. Lymphoid tissue readily undergoes hyperplasia as the result of local irritation. Compensatory hyperplasia is seen in the bone-marrow which so readily



FIG. 103.—Compensatory hypertrophy of one kidney.

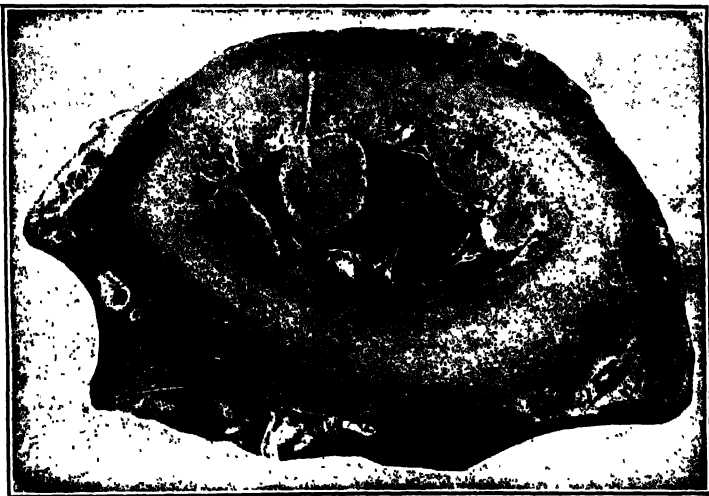


FIG. 104.—Concentric hypertrophy of the left ventricle in aortic stenosis.

becomes hyperplastic when there is a demand for more blood. When a portion of the thyroid gland is removed the remaining tissue undergoes marked hyperplasia so as to compensate for the loss. The liver also has remarkable powers of compensatory hyperplasia.

## MALFORMATIONS

The subject of malformations, maldevelopment, and monsters is an extremely large one, involving as it does a study of all the possible errors which may occur during the complex process of development. The scope of this work, not to mention the lack of knowledge of the writer, makes any attempt to cover the subject out of the question. All that will be attempted will be to give a catalogue of the principal conditions, so that the student will at least become familiar with their names. If he wishes to enquire into the rationale of the various malformations he may consult Adami's *Principles of Pathology*, or the monographs by Ballantyne and Schwalbe. For convenience the subject may be divided into: (1) maldevelopments, inclusions, etc.; (2) local malformation; (3) double monsters.

**Maldevelopments.**—Many minor errors of development are compatible with life and even with health. Most of these will be described when diseases of the individual organs are discussed. There may be too few digits or too many (supernumerary). Two or more of the fingers or toes may be fused together, a condition of *syndactyly*. The kidneys may be fused at the upper or the lower pole, the horseshoe kidney. Remnants of fetal structures which normally disappear may remain, *e. g.*, Meckel's diverticulum, Wolffian ducts, thyroglossal duct, ductus arteriosus, etc. The congenital anomalies of the heart form a subject in itself. In the course of development portions of an organ may become detached and included in another organ. Thus inclusions or "rests" of adrenal cortex may be found in the kidney and the pelvic organs, pancreatic tissue occurs in the wall of the stomach and duodenum, thyroid tissue at the base of the tongue and elsewhere in the neck. This displacement of tissue is called *heterotopia*. Along the normal lines of closure of developmental clefts dermal tissues may be infolded and included in the underlying structures. The included tissue may start to grow, forming an *inclusion dermoid*. These lesions are commonest in the face and the middle line of the body both anteriorly and posteriorly. It is possible that certain tumors of mixed structure (parotid and kidney tumors) may arise from these inclusions.

**Local Malformations.**—During normal development a number of grooves and fissures must be accurately closed. If any of these remain open either wholly or in part grave malformations may result. These may be reviewed briefly.

**Neural Groove.**—The entire groove may remain open, but usually the deficiency is only partial. If the cranial part is open the condition is called *cranioschisis*; if the spinal part is unclosed it is called *rhachioschisis*. In *cranioschisis* the brain may be absent save for an amorphous mass of tissue on the floor of the cranial cavity, a condition of *anencephaly* or *acrania*; the child is an *anencephalic monster*. The frontal part of the cranium may be closed, while the occipital part remains open and the brain hangs out at the back. When the patency is more limited in extent there may merely be some prolapse of the meninges or the brain covered by skin—*meningocele* or *encephalocele*. In the spinal canal by far the commonest defect is *spina bifida*, the lowest part of the canal remaining unclosed. Here also there may be *meningocele* or *meningomyelocele*.

**Sternal Fissure.**—If the patency is at all marked extra-uterine life is impossible, for the lungs are unable to expand. The heart may protrude through the opening, a condition of *ectopia cordis*.

**Abdominal Fissure.**—The two halves of the abdominal wall may fail to close. There will then be eventration or protrusion of the viscera.

**Urogenital Fissure.**—The bladder may be extruded or it itself may fail to close, a condition of *ectopia vesicæ*. If the urethra does not close it is represented by a groove on the dorsal surface of the penis or clitoris, a condition of *epispadias*.

**Facial Clefts.**—If there is gross failure of the various facial clefts to close, the fetus will be a monster. Very much commoner is *harelip* and the often associated *cleft palate*. The maxillary process fails to unite with the intermaxillary bone and the defect may be limited to the lip or may extend back into the hard and even the soft palate. The lesion may be unilateral or bilateral. If the intermaxillary bone is absent there will be a median cleft palate.

**Branchial Clefts.**—The branchial clefts below the first (which forms the Eustachian tube) may remain open. The third is the most frequently involved. The entire cleft may remain open, constituting a *branchial fistula* which connects the pharynx with the skin surface of the neck. The outer end may remain open; this is a *branchial sinus*. The commonest lesion is a *branchial cyst*, in which both ends are closed, but the intermediate portion remains open.

**Rectal Malformations.**—There may be a *persistent cloaca*, in which the rectum fails to be separated from the external genitalia. If partial separation occurs a *fistula* is formed, the rectum communicating by a passage with vagina, bladder or urethra. The septum which separates the skin from the hind gut may not be broken down as normally occurs; this is a condition of *imperforate anus*.

**Double Monsters.**—Monsters may be single or double. Instances of single monsters have already been given, although of course it is not always easy to say when a defect is sufficiently severe to justify the use of the word monster. One form has not yet been mentioned. The two eyes may be fused so that there is a single eye in the center of the forehead. The condition is known as *cyclops*, named of course after Polyphemus in the *Odyssey*. Double monsters are an anomaly of twin formation. They may be symmetrical or asymmetrical.

**Symmetrical Monsters.**—In these, two individuals are joined together. The union may be in the head region, in the thoracic region, or in the sacral region. (1) *Craniopagus* is fusion in the head region. The fusion often only involves the scalp and cranium. There may be two faces looking in opposite directions. Or there may be a single head, the two bodies remaining separate. The position may be reversed, the bodies being fused into one, while the heads remain separate. There is then a two-headed monster or *dicephalus*. (2) *Thoracopagus* is fusion in the thoracic region, the remainder of the two bodies remaining separate. There may be a common thoracic cavity with a double set of viscera. Sometimes there is only union between the ensiform cartilages and the surrounding soft parts. Such a condition is quite compatible with life, and it was in this way that the Siamese twins who lived to the age of sixty-three years were united. (3) *Ischiopagus* is fusion in the pelvic region. The head, thorax, and spinal column of each individual remain separate, but there is union below the umbilicus and a pelvic ring in common. In the above description only the main types of symmetrical double monsters have been mentioned. There are endless variations.

**Asymmetrical Monsters.**—1. *Unequal Twins.*—As a rule, both twins develop equally. But one may die and be converted into an amorphous lump of flesh. In other cases the fetus is fairly well developed, but the heart is poorly developed or rudimentary. This is an *acardiac fetus*. In such cases the course of the circulation has been reversed; the *acardiac fetus* is nourished by the blood of the other twin, so that the heart, having little to do, does not develop.

2. *Parasitic Fetus.*—This is an example of a double monster in which the development of one of the twins is arrested. This twin does not die as in the case of unequal twins, because it is united with the other twin upon which it lives as a parasite. The parasite may be attached in the cranial, thoracic, or pelvic region, giving a *parasitic craniopagus*, *parasitic thoracopagus*, or *parasitic*

*ischiopagus*. The parasite may be fairly well developed or may be a mere jumble of tissues. When such a rudimentary mass is attached to the mandible it is called an *epignathus*. It may be attached to the sacrum, forming a *sacral teratoma*.

3. *Congenital Teratomata*.—As already indicated, the parasitic mass may be unrecognizable as a separate individual, consisting merely of a confused mass of tissues such as brain, bone, cartilage, teeth, skin, hair, and glands. This may be attached to the exterior of the body, most often in the sacral region, or it may be included in the body cavity (mediastinum, ovary, testicle, etc.). These are congenital teratomata or dermoids, so-called because they contain dermal structures. They are to be distinguished from the teratomata which develop in adult life, usually in the ovary, more rarely in the testicle, and which are probably derived from segregation of one of the blastomeres of the developing ovum.

#### ADDITIONAL READING

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## CHAPTER X

### TUMORS

A TUMOR or neoplasm may be defined as a growth of new cells which proliferate without control and which serve no useful function. Most tumors are easy enough to recognize, but on the outskirts of the group there are tumor-like masses regarding which no one can say with certainty whether or not they are true neoplasms. Two common examples are leukemia and Hodgkin's disease.

The differentiation between neoplastic and inflammatory conditions is usually easy. In inflammation the causal organisms can be demonstrated, the inflammatory cells which may constitute a lump or mass are varied and pleomorphic, and in course of time the lesion clears up. In a true neoplasm the cells are usually all of the same type (epithelial cells, fibroblasts, etc.), and the condition is progressive. But the matter is not quite so simple. The cells of a tumor may be very pleomorphic (osteogenic sarcoma, glioblastoma multiforme), and on the other hand a chronic inflammatory condition may show marked cellular proliferation. Repair, indeed, is just proliferation, and it may be hard to say where the proliferation of repair ends and the proliferation of neoplasia begins. These considerations have a twofold importance. In the first place they suggest that it may be unwise to draw too strict a line between inflammation and neoplasia, so that there may be borderland conditions such as Hodgkin's disease which partake of the character of both. In the second place it is possible that the hyperplasia of chronic inflammation may cross the line and become the hyperplasia of tumor growth.

### INNOCENT AND MALIGNANT TUMORS

It is easy to divide tumors into two great classes: the one innocent, simple or benign, the other malignant. This is true both for epithelial and connective-tissue tumors. In the former carcinoma and in the latter sarcoma is the malignant representative. All malignant tumors are included under the common heading of cancer, meaning a crab, from the claw-like processes which characterize these growths. But once again difficulty is experienced when the typical center of the group is left and the indefinite margins are approached. If we proceed far enough we find ourselves confronted with the question as to whether an innocent tumor, epithelial or connective tissue, can become converted into a malignant one. An innocent tumor seldom changes its character, but occasionally it may do so. A papilloma of the colon or rectum often becomes a carcinoma, a fibroadenoma of the breast

may become a sarcoma, a pigmented mole may become a malignant melanoma.

The *characteristics of malignancy* are as follows.

1. A malignant tumor if untreated will *kill* the patient wherever it grows, even in the hand or the foot. An innocent tumor will only cause death if it happens to grow in a vital organ.

2. A malignant tumor *infiltrates* the surrounding tissue. It sends claws into it like a crab. An innocent tumor, on the other hand, grows by expansion, and is usually separated from the surrounding tissue by a capsule.



FIG. 105



FIG. 106

Figs. 105 and 106.—Mitotic figures. Fig. 105 shows the monaster stage (metaphase) and Fig. 106 the diaster stage (anaphase).  $\times 700$ .

3. When a malignant tumor is removed it may *recur*. This may be due to one of two causes. (1) Usually the reason is that some of the



FIG. 107.—Atypical mitosis. The chromosomes have divided into three groups in the center. Three centrosomes and attraction spheres are also seen.  $\times 1500$ .

original growth has not been removed. Cancer cells may lie dormant for years and then may start to grow. Sometimes the so-called recurrence is not at the primary site, but at some distant point to which the malignant cells have been carried. Thus cancer of the breast may "recur" in the lung as much as twenty years after complete removal of the primary tumor. (2) There may be a fresh development of new cancer cells at the original site, arising from cells which were not at first cancerous, due possibly to persistence of the original cause.

4. A malignant tumor, as a rule, grows rapidly, so that *mitotic figures* may be seen. (Figs. 105 and 106.) The more rapid the growth, the more numerous are the mitoses. The mitotic figures seen in ordi-

nary sections of pathological tissue are not like those of the histological textbook. When the nucleus of a tumor cell is represented by a dark mass of chromatin, the cell is probably undergoing mitotic division. If the chromatin is collected as a bar across the center of the cell (monaster, metaphase) or in two separate masses, one at each pole (diaster, anaphase), the probability becomes a certainty. In malignant tumors atypical mitosis (multicentric division) may sometimes be seen. (Fig. 107.) Colchicine has a remarkable power of arresting mitosis, which is of value in experimental work. It must be remembered that mitosis is also present in rapidly-growing granulation tissue, and in any other rapidly regenerating tissue. It is evident, therefore, that the presence of mitoses is no proof of malignancy. This is particularly true of connective-tissue lesions. Some cancers grow slowly, but in others one can almost watch the increase in size from day to day. I have seen an abdomen opened, revealing a tumor of the ovary which biopsy proved to be carcinoma. The abdomen was again opened three weeks later (the delay being due to an intercurrent infection), and the entire peritoneum was now found to be covered with cancer.

5. A malignant tumor sets up secondary growths or metastases in lymph nodes and in distant organs. Some malignant tumors, *e. g.*, gliomas, do not behave in this way.

6. A malignant tumor fails to reproduce the structure of the tissue from which it grows. The greater the failure the more undifferentiated or *anaplastic* is the tumor said to be, and the more malignant is its nature. An innocent tumor may reproduce glandular and other structures with perfect fidelity, *i. e.*, differentiation is complete. When the cells fail to show a normal relationship to their neighbors they are said to show *loss of polarity*.

In deciding the all-important question of the malignancy of a tumor it is necessary to consider not only the histology (arrangement of the cells) but also the cytology (character of the cells, especially their nucleus and nucleolus). The most vital function of a cell, the reproduction of its proteins, is regulated by the nucleus, and in particular by the nucleoproteins of the chromatin. Ultra-violet spectroscopy shows that there is intense activity



FIG. 108.—Smear of cancer of breast showing irregular cells and large nucleus and nucleolus.  $\times 500$ .

of this mechanism in cancer cells. It seems probable that the increased rate of cell division in cancer associated with abnormal chromosome behavior may be explained in terms of disturbed nucleic acid metabolism (Koller). Irradiation interferes with this mechanism, and may lead to death of the cancer cell. The malignant nucleus is large, hyperchro-



FIG. 109, Grade 1.



FIG. 110, Grade 2.



FIG. 111, Grade 3.

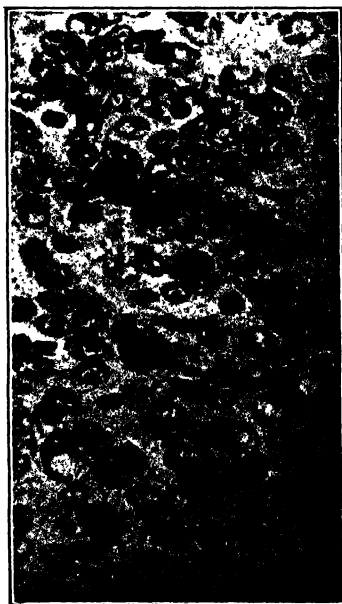


FIG. 112, Grade 4.

FIGS. 109 to 112.—The four grades of epidermoid carcinoma.

Differentiation is complete in Fig. 109; Fig. 112 is extremely anaplastic with many mitotic figures. Fig. 109,  $\times 200$ ; Fig. 110 to 112,  $\times 500$ .



matic (the chromatin stains deeply) or with coarse network, varies much in shape, and is generally eccentric. The method of microincineration shows that the inorganic content of the nuclei of malignant

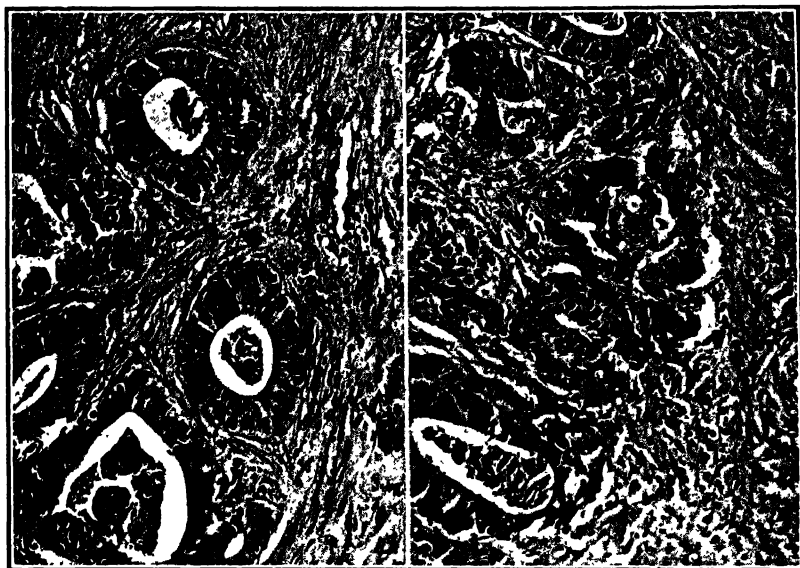


FIG. 113, Grade 1.

FIG. 114, Grade 2.

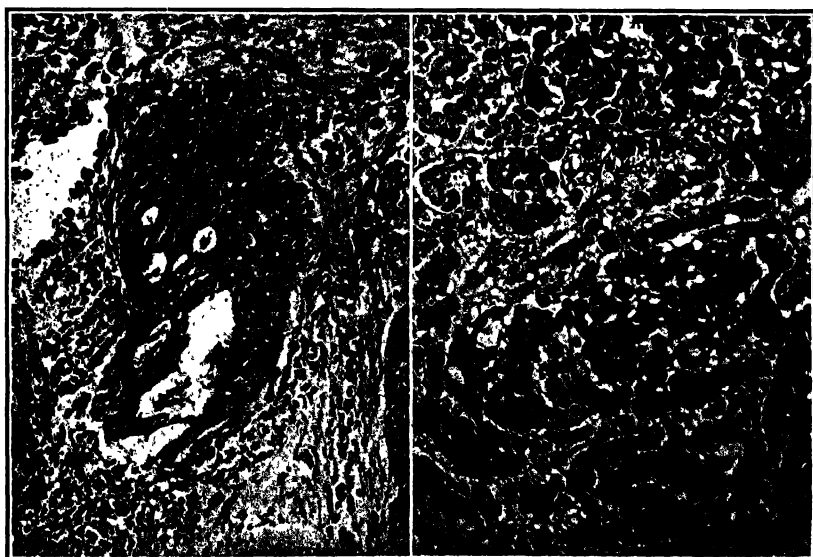


FIG. 115, Grade 3.

FIG. 116, Grade 4.

FIGS. 113 to 116.—The four grades of adenocarcinoma.  $\times 125$ .

cells is higher than that of normal cells (Scott and Horning, Cathie). The most important single feature, as MacCarthy has emphasized, is the nucleolus, which is much larger in proportion to the nucleus than in a normal cell or in the cell of a benign tumor, and is surrounded by a clear halo. These cytological features are best seen in frozen sections of unfixed tissue, or in wet films rapidly fixed and stained. (Fig. 108.) Fidler, on wet films in my laboratory in Winnipeg, found that multinucleated cells and giant cells were present much more frequently than in paraffin sections from the same tissue. He points out, however, that the above criteria are only true for carcinoma, not for sarcoma.

**The Grading of Tumors.**—A tumor may show any degree of malignancy. It is easy to make a microscopic diagnosis of a highly malignant tumor, but to tell if a tumor of low malignancy is really malignant may be very difficult, a fact which the clinician must bear in mind. Moreover the degree of malignancy has an all-important bearing on the prognosis and on the prospect of successful treatment. For this reason Broders has introduced a system of grading malignant tumors, dividing them into four groups according to their apparent malignancy and probably prognosis. (Figs. 109 to 112 and Figs. 113 to 116.) Grade 4 is the most malignant (like the 4+ Wassermann), Grade 1 the least. The points taken into consideration are: (1) absence of differentiation (anaplasia), (2) hyperchromatism (nuclei rich in chromatin), and (3) the number of mitotic figures. (Figs. 109 to 112.) In epidermoid carcinoma, in which the method was first worked out, it is found that with adequate treatment the prognosis in Grade 1 is excellent, while in Grade 4 it is practically hopeless. Grading is a useful method of communication between pathologist and surgeon, and an indication to the latter of the probable prognosis. It can also be used as a guide to treatment, Grades 1 and 2 being suitable for operative removal and Grades 3 and 4 for radiation. From the pathological standpoint there is, of course, nothing new in distinguishing between different degrees of malignancy in a tumor, for it was in 1893 that Hanseman first introduced the concept of anaplasia.

But there are limits to the value of grading which must be recognized. It is of most value in carcinoma of the skin and carcinoma of the rectum where differentiation is easy to recognize (cornification, gland formation), it is difficult in cancer of the breast and the cervix uteri, and it is useless in the malignant melanomas. Moreover it must be realized that a tumor may not show a uniformly malignant structure in every part and that a small portion removed for biopsy may be misleading. Finally, microscopic grading must not take the place of careful clinical judgment, for the latter may offer a better chance of arriving at a correct prognosis. The clinician must not take grading too seriously, but must consider the age of the patient, the extent of the disease, its duration, its rate of growth, and most important of all, involvement of lymph nodes. He is apt to think that the chief value of grading is an aid to prognosis. This is not the case, for it may be

quite deceptive. The histological character of the lesion does not necessarily parallel the biological tendency which we designate as malignancy. The real value of grading lies in the indication which it gives as to the radio-sensitivity of the tumor. It is a guide to treatment rather than to prognosis.

### BIOLOGICAL DISTURBANCES IN MALIGNANCY

The biological study of tumors includes both the metabolism of tumor cells and the general constitutional disturbances. The study of the metabolism of the tumor cell is of fundamental importance, because by means of it we are more likely to come to an understanding of what a neoplasm really is and in what respects it differs from normal tissue.

**Glycolysis.**—The most important work on cell metabolism is that of Warburg, who has studied the metabolism of isolated tissues *in vitro*. Tiny pieces of living tissue are placed in a special chamber in Ringer's solution containing sodium bicarbonate and glucose. Any acid formed from the glucose will react with the bicarbonate to form carbon dioxide; this is measured and indicates the amount of glucose consumed. There are two phases of tissue metabolism, two possible sources of energy and life. These are: (1) *respiration*, the aerobic burning of glucose to form carbon dioxide and water; (2) *glycolysis*, the anaerobic breaking-down of sugar into lactic acid without the consumption of oxygen. In the absence of oxygen all tissues can produce lactic acid from glucose, but adult tissues depend on respiration and respiration prevents glycolysis. The cancer cell does not need oxygen. It has extraordinary glycolytic powers, and in ten hours can destroy its own weight of sugar and convert it into lactic acid. It is like an asphyxiated cell of normal tissue. Benign tumors and embryonic tissue behave like malignant tumors under anaerobic conditions (glycolysis), but like adult tissue under aerobic conditions (respiration and oxidation). Curiously enough the retina and the gray matter of the brain have the same high glycolytic rate under anaerobic conditions as tumors.

**The Blood.**—*Anemia* of a secondary type is often marked, especially in ulcerating tumors. In cancer of the stomach the anemia may be of the pernicious or primary type. Several factors may cause the secondary anemia. Of these hemorrhage is the most obvious. Secondary involvement of the bone-marrow sometimes plays a part. It is probable that the absorption of toxic substances which act on the hemopoietic apparatus is the most potent factor. *Leucocytosis* often occurs, but can generally be attributed to the accompanying sepsis. None of the blood changes is pathognomonic of malignancy.

**Fever.**—It is unfortunate that fever, sometimes long continued, may occur in malignant tumors, because it adds grave difficulties to the clinical diagnosis. Here again there is more than one cause. Septic infection may or may not be accompanied by fever. But there may be fever without any infection, especially in hypernephroma of the kidney, in malignant tumors of bone (osteogenic sarcoma, Ewing's tumor), and in primary carcinoma of the lung. In these cases fever-producing proteins must be absorbed from the tumor into the blood stream.

### METHODS OF SPREAD OF TUMORS

Innocent tumors do not present any special problem of spread. They grow expansively and compress the tissues in their neighborhood so that some sort of capsule is often formed. It is otherwise with malignant tumors. The process is best studied in carcinoma which may spread in the following ways.

1. **Infiltration.**—Carcinoma cells tend to *grow into connective tissue spaces* and to invade lymphatics. This is because there is less resistance in the connective tissues than in a solid sheet of epithelium. At the edge of the tumor the cells can be seen growing along the tissue spaces to a great distance so that the microscopic area of the tumor is much larger than the gross area, and it is the microscopic area which the surgeon has to consider.

There may be *permeation of the lymphatics*, a method of spread especially emphasized by Sampson Handley in cancer of the breast. Here the tumor invades the lymphatic vessel and grows along it.

There may be an *intra-epithelial spread* of carcinoma. This is uncommon because the solid epithelium offers more resistance and less nutriment than the more open connective tissue. There may be spread from an underlying tumor into the epidermis, the carcinoma cells making their way between the normal epithelial cells and often degenerating and leaving vacuoles. This is what happens in Paget's disease of the breast where the underlying tumor is a duct carcinoma. If the tumor cells produce some readily-stainable material such as mucin the process is more readily recognized (Dunn). In rare cases a basal-cell carcinoma may spread through the epidermis rather than invade the deeper tissues. All of these are of uncommon occurrence, for a carcinoma is much more apt to destroy the epidermis than to infiltrate it.



FIG. 117.—Multiple foci of independent growth in a rodent ulcer.  $\times 45$ .

What may be called the *contact spread* of cancer is of great theoretical interest. If an innocent papilloma of the colon which is becoming malignant be studied it will be observed that at the point of junction every variation may be seen between a typical cancer cell with hyperchromatic nucleus and an innocent goblet cell. In the same gland there may be representatives of what are apparently both innocent and malignant cells. I have observed the same phenomenon in the skin, where the result may be multiple malignant foci arising in a limited area (Fig. 117). A precancerous change seems to affect the normal cells before the tumor actually reaches them, as if some malignant wave had spread along the surface.

PLATE V



Tumor Emboli in Bloodvessels in Wall of Intestine.



2. **Embolism.**—Tumor cells may be carried to a distance by the lymph or the blood stream. *Lymphatic embolism* causes secondary growths in the regional lymph nodes, usually in those nearest the primary tumor but sometimes at a distance; thus cancer of the stomach may infect the supraclavicular glands. Carcinoma commonly spreads by the lymph stream, sarcoma rarely.

Embolism by the *blood stream* is common in both carcinoma and sarcoma. (Plate V and Fig. 118.) Highly vascular tumors and those which tend to invade bloodvessels are prone to cause early metastases. Perhaps the best example is chorionepithelioma of the uterus. Tumors in the systemic circulation (bones, kidneys) tend to infect the lungs, those in the portal circulation (stomach, colon) tend to infect the liver. Primary cancer of the lung infects the brain and other viscera. But there is often no apparent rhyme or reason about the dissemination of tumor cells. In one cancer of the stomach the liver is a mass of metastases, in another the spread is entirely to the abdominal lymph nodes, while in a third there may be no apparent spread beyond the stomach.

The question of suitable environment must play an important part. The muscles must be flooded with cancer emboli, and yet a secondary growth in muscle is the rarest occurrence. Tumor emboli in the lungs often die out, as M. B. Schmidt showed many years ago. They become coated with fibrin, the tumor cells are never properly implanted and fail to develop

into metastatic growths. If in two animals with the same type of tumor the tumors are massaged and one animal is killed soon afterward, the lung capillaries will be found to be stuffed with tumor cells. If the other animal is killed some months later only a few metastases will be found in the lungs. Most of the emboli have failed to develop. Oertel points out that there may be widespread embolic plugs of tumor cells without the formation of metastases, thus distinguishing between transportation and true secondary growths due to the cells breaking through the walls of the vessels and "taking." Some tumors have a special predilection for certain organs. It is not because they are specially carried there, but because they find a suitable environment. Secondary tumors of bone are likely to have come



FIG. 118.—Tumor embolus in a bloodvessel.  
× 375.

from the breast, the prostate, the kidney, the lung, or the thyroid; those in the skin commonly come from a melanoma.

Metastases are not always found in those organs where they might be expected on strictly anatomical grounds. Cancer of the prostate may metastasize to the cervical vertebræ and to the long bones although no secondary tumors may be present in the lungs. Paradoxical embolism through a patent foramen ovale and other fanciful explanations have been suggested to account for this phenomenon. The work of Batson appears to provide the true explanation. By means of injections followed by radiography Batson has demonstrated a system of veins, which he names the *vertebral system*, passing up inside the spinal canal and anastomosing with sacral, lumbar, abdominal and thoracic veins, as well as with veins penetrating the vertebral bodies and cranial bones and cavity. Similar veins have been described and figures by the older anatomists. In animal experiments it was possible to show that there were frequent reversals of flow in this vast intercommunicating system the result of coughing, straining, and increase of intra-abdominal pressure. During these reversals a pathway up and down the spine exists which does not involve the heart and lungs, a system which is more a venous pool or bypass rather than a vein with a constant flow of blood. As flow takes place into the system during coughing, it is easy to understand the high incidence of cranial metastases in cancer of the lung and secondary brain abscesses in lung abscess. There are thus four systems of veins by which tumors may spread to a distance, the caval, pulmonary, portal and vertebral veins.

Metastases may exactly duplicate the primary tumor, but in some cases they present a different picture. They may be more or less differentiated than the primary growth. It is sometimes easier to make a correct histological diagnosis from a secondary growth in a lymph node than from the primary tumor.

*Multiple tumors* are often a puzzle. It may be difficult to know if the tumor has started at one spot and has then metastasized, or if the various growths are of multicentric origin. Multiple myeloma of bone and lymphosarcoma provide examples of this problem. *Multiple primary malignant tumors* are common in the skin, and fairly common in the intestinal tract. Occasionally there may be primary tumors of more than one organ.

The student may be surprised to learn that it sometimes happens that at autopsy numerous tumors are found which are apparently all secondary, yet careful search may fail to reveal a primary growth. In such cases a small primary nodule may have been overlooked in such locations as the nasopharynx, male breast, prostate or bronchus.

3. **Implantation.**—Secondary growths may be scattered over a serous or a mucous surface owing to tumor cells being seeded on the surface and gaining a hold. Good examples are carcinoma of the ovary infecting the peritoneum and papillary carcinoma of the bladder causing secondary growths in other parts of that organ.

The question of *tumor inoculation* is of surgical interest. The danger



of tumor cells being implanted in the surrounding tissue during the course of a biopsy is more apparent than real. Still the danger is there, and the best way to remove a piece of tissue for microscopic examination is by means of the electrocautery which kills the tumor cells with which it comes in contact.

### THE EFFECTS OF TUMORS

The effect produced by a tumor depends on the site of the tumor and its nature. An innocent tumor causes pressure atrophy of the surrounding parts. A malignant tumor produces active destruction of tissue partly by direct pressure, partly by interfering with the blood supply. A skin or mucous surface becomes ulcerated and infection follows. When the tumor comes in contact with bone it causes erosion. Erosion of a vessel will lead to hemorrhage, a very common symptom in cancer of the uterus, stomach, and bowel. A natural passage may be occluded with dilatation of the proximal part; in this way there may be great dilatation of the stomach, common bile duct, and cerebral ventricles. The general constitutional effects have already been described in connection with biological disturbances.

The *cause of death* is varied. If the tumor grows in a vital organ the cause is obvious. Sepsis may play an important part. In cancer of the esophagus death is due to starvation. Often we can only name malignant cachexia and exhaustion.

**Spontaneous Cure.**—At any time an innocent tumor may stop growing, whereas a malignant tumor continues to grow as long as the patient lives. There are many reports in medical literature of spontaneous cures of malignant disease but very few of these will bear careful scrutiny. No case can be admitted unless the diagnosis has been confirmed by biopsy and unless a complete postmortem examination has been made. These conditions have seldom been fulfilled. The following special cases deserve consideration. In chorionepithelioma removal of the primary tumor in the uterus may be followed by disappearance of secondary growths in the lungs. Partial removal of an adenocarcinoma of the ovary has been followed by complete recovery. In rare cases of cancer of the breast with secondary growths, several of the tumors may disappear and the patient may live in good health for a number of years, though eventually dying of the disease. The interest of these examples is that they suggest the development of an immunity which is at least partially successful. If only we could do something to make the success complete!

### THE ETIOLOGY OF TUMORS

Whilst it is true that the essential *nature* of cancer remains a biological mystery, a vast amount of information has been collected concerning factors relating to its *causation*. At the outset of this discussion it may be said that cancer can be caused in the experimental animal and that it can be cured in man. In spite, therefore, of our ignorance regarding the nature of the intracellular change it is perhaps time that we stopped describing cancer as an unsolved riddle. The bulk of the newer knowledge comes from experimental work on animals, but clinical observations of fundamental importance have been made

in the past and will continue to be made in the future on human material.

The public and the press are fond of speaking about "the cause of cancer." This is natural if cancer be regarded as a disease entity like tuberculosis, although even in the case of tuberculosis the tubercle bacillus is not of itself sufficient to produce the disease. But cancer may be regarded as a group of diseases, comparable with the infective fevers; if this is correct there may be different causes for cancer of the breast, cancer of the stomach, and cancer of the brain. Or malignant disease may be considered as a type of reaction to a variety of stimuli, just as is inflammation; some of these stimuli may be physical, some chemical, some hormonal, some bacterial, and some viral. Once started, the process may be irreversible and possess common characteristics dependent on the nature of living matter, no matter how varied the exciting agents may be.

The onset of cancer is not a bolt from the blue. In experimental tumors, and in some human tumors whose development can be observed, there is a long period of preparation, during which a gradual change is taking place. At the end of this time a sudden change seems to occur, as a result of which the normal cell is changed into a malignant cell with fundamentally different properties. This process is discontinuous in character, new, strange, abrupt and irreversible. The transformation is as strange as the sea-change described in *The Tempest*.

Malignant cells are not simply cells which have acquired rapidity of growth. They are specifically altered cells, and the specific characters may remain unaltered for thirty years, whether the cells are propagated by transplantation or grown as tissue cultures. Normal chick fibroblasts can be grown for years in culture, but when finally inoculated into chicks they cease to grow; cancer cells, on the other hand, grow when inoculated after years of culture.

The first phase of experimental carcinogenesis may correspond to what clinicians call a *precancerous condition*. This may be defined as a condition in which cancer subsequently arises with a high degree of frequency. In human cancer it is not based on histological criteria, because the morphological changes by which cancer is recognized have not yet taken place. Precancerous lesions, either neoplastic or inflammatory, although apparently benign, develop into cancer with greater frequency than does normal tissue in the same location. Examples of such lesions are benign moles and multiple papillomas of the large bowel. It may be said that prolonged stimulation of cell division such as is seen in hyperplasia and chronic irritation is a prerequisite to the successful operation of the factors described below. A great variety of factors may be responsible for the first phase, and these are known as *carcinogenic agents*, although it is evident from what has been said that the strict accuracy of the term is open to question. They may be termed more appropriately the *preparatory cause*. The *exciting cause* which is responsible for the change of the normal (though prepared) cell into a malignant cell is the real mystery of cancer. The

*preparatory* cause may be an *exogenous* factor operating from without or an *endogenous* factor derived from substances formed normally by the body and possessing definite physiological functions. Both of these groups are *carcinogenic agents*, although the term is often limited to the first group.

**Exogenous Carcinogenic Agents.**—The truism most often heard in connection with the production of cancer is that *chronic irritation* is a potent factor. Much clinical evidence is adduced in support of this statement. Well known examples are cancer of the lip and heavy smoking, cancer of the tongue and a jagged denture or syphilitic glossitis, cancer of the gall bladder and gall stones. X-ray workers are apt to develop cancer of the skin, and bones which have become highly radio-active owing to the person swallowing radio-active luminous paint may become the seat of a malignant growth. Osteogenic sarcoma develops in the bones of rats as the result of feeding the animals minute quantities of radium (Dunlap *et al.*). A striking example is cancer of the abdominal wall in the natives of Kashmir who carry a hot basket of charcoal, the kangri, under their clothes for purposes of warmth; it is striking because cancer in this part of the body is extremely rare.

But an irritant is by definition an agent which excites inflammation. Carcinogenic substances such as tar and oil are soothing substances, whereas irritants such as acids and alkalis never cause cancer. Some compounds which are irritating do not produce cancer, while their isomers, which may be non-irritating are carcinogenic. A very slight change in the chemical structure of a substance may convert it from a non-carcinogenic into a carcinogenic agent.

The first observation on chemical carcinogenic agents was that of Sir Percival Pott in 1775, who noticed that cancer of the skin was especially common in men who worked with tar and he offered the suggestion that the tar acted in some manner as a causal agent. This may be linked with a recent observation that cancer of the lip is especially common among fishermen on the west coast of Scotland, who, in mending their nets, put the bone needle threaded with tarred twine between their lips. In 1915, that is to say one hundred and forty years after Pott's paper, Yamagiwa in Japan put this idea to the test by painting tar on a rabbit's ear every day for six months, and succeeded in producing cancer of the skin. This was an epoch-making discovery, because for the first time it was possible to produce a malignant tumor at will. All previous experimental work had consisted of transplanting tumors which occurred spontaneously in animals. Subsequent work has shown the mouse to be a much more suitable animal than the rabbit.

Tar is a highly complex substance containing a great variety of chemical agents. The next step was to determine the active agent or agents present in tar which were responsible for producing the cancer. This step was taken by Kennaway and Cook in 1932, when they succeeded in isolating the hydrocarbon benzpyrene from tar and showed that it possessed a high degree of carcinogenic activity. It was then

noticed that benzpyrene gave a spectrum with fluorescent light very similar to that of a group of recently synthesized hydrocarbons, of which one of the important members is 1:2:5:6 dibenzanthracene. On following up this lead it was at once found that the latter substance was powerfully carcinogenic, and as it had the advantage of being a chemically pure substance of known composition, it has become the most popular agent in the experimental production of cancer. It is interesting to note that 1:2 benzanthracene has practically no carcinogenic activity, but the attachment of a new benzene ring in the 5:6 position gives it great carcinogenic power.

Another of the chemical carcinogenic compounds is the cholanthrene group. Cholic acid, an organic substance occurring *naturally* in the body, can be converted by chemical means into methylcholanthrene, a hydrocarbon related in structure to the *synthetic* hydrocarbons which have just been described. On trial it was found that cholanthrene and methylcholanthrene were amongst the most powerful carcinogenic agents known. It is the presence of the five-membered ring, known as the pentacyclic system, not the methyl group, which confers on the compound its carcinogenic power. When this substance is painted on the skin it produces carcinoma, when injected subcutaneously it produces sarcoma. It will be observed that both methylcholanthrene and benzpyrene, the original carcinogenic substance isolated from tar, contain the 1:2 benzanthracene ring system, although that system itself is almost completely lacking in activity.

It used to be thought that long-continued application of a carcinogen was necessary for the production of cancer. Cramer and Stowell, however, have shown, that a single application of methylcholanthrene with one brush stroke to a susceptible animal is sufficient.

To summarize this brief review of the chemical carcinogenic compounds, three main groups may be recognized. (1) Benzpyrene, the original carcinogenic hydrocarbon isolated from tar. (2) The benzanthracene group; 1:2 benzanthracene is practically inert, but 1:2:5:6 dibenzanthracene is extremely potent. (3) The cholanthrene group, which is benzanthracene with the addition of a five-membered ring.

Any of these agents can produce either carcinoma or sarcoma at the site of application. If applied to an epithelial surface carcinoma develops, if injected subcutaneously sarcoma is the result. By this means it has been possible to produce carcinoma of the skin, kidney, liver, testis, bladder, and uterus, as well as sarcoma of the subcutaneous tissue and peritoneum. Brain tumors (gliomas) can be produced by the intracerebral implantation of pellets of methylcholanthrene. It is of great interest to note that when embryonic tissues are transplanted with a crystal of methylcholanthrene to adult animals they become carcinoma or sarcoma in from one to two months (Greene).

When fibroblasts from the rat or mouse are grown in tissue culture in a medium containing a powerful carcinogenic chemical, such as methylcholanthrene, they are changed into cells which are similar to the cells in cultures of sarcoma induced by injection of the carcinogen

into subcutaneous tissue (Earle and Voegtlin). Moreover sarcoma can be produced by the injection of cells so treated (Earle). The change is irreversible. It is not difficult to make normal cells and their descendants cancerous either *in vitro* or *in vivo*. Unfortunately we have not yet learned how to make cancerous cells normal again.

It has long been believed that the carcinogenic agent had to act for a prolonged period of time in order to produce its effect. In 1939, however, Mider and Morton showed that a single application of methylcholanthrene can cause skin cancer, and more recently Cramer and Stowell found that single applications of methylcholanthrene at intervals of several weeks produced cancer with smaller doses than when the classical continuous method was used. They suggest that injury to the epithelium results in the liberation of substances which stimulate the cells to proliferate over a prolonged period.

It must not be supposed that the only potent carcinogenic agents are the hydrocarbons. Clinical observation has long shown that arsenic has carcinogenic power when taken as a medicine for too long a period. So simple a substance as zinc chloride can induce the growth of so complicated a tumor as a teratoma when injected into the testicle of a rooster. The spirocheta pallida is well known to act as a carcinogenic agent when located in the tongue.

A carcinogenic agent of extraordinary potency was discovered by accident in the course of testing the toxicity of a new insecticide acetyl acetaminofluorine. This substance when implanted in the tissues causes neither inflammation nor tumors, but when given by mouth to rats it produces cancer of the liver, pancreas, breast, bladder, lung and salivary glands, as well as sarcoma and leukemias (Bielschowsky). The thyroid escapes, but when the chemical is combined with thiourea, which itself produces intense hyperplasia but no cancer, the result is carcinoma. This seems to indicate that hyperplasia, whether or not caused by chemical carcinogens, appears to be a necessary factor in the development of cancer.

It might be supposed that the exogenous carcinogens directly stimulate the cells to multiply. This is not the case. Such agents as dibenzanthracene first produce destruction of cells, which is followed by repair (Wolbach). There is a period of hyperplasia, which precedes tumor development. It is not possible to trace the transformation of normal into malignant cells. A new race of cells appears quite suddenly in the area involved. Murray and Woglom have demonstrated the interesting fact that the tissue may apparently be malignant before any structural change can be detected. They tarred a mouse for four months; at the end of that period the skin showed no change. The epithelium was then removed and transplanted into another animal, and typical carcinoma developed.

The experimental work with the exogenous carcinogens agrees with clinical observation that those exposed to certain external agencies are liable to develop cancer of external parts. Persons exposed for long periods to brilliant sunshine or inclement weather may develop cancer

of the skin. The same is true of workers with x-rays and radium. Chimney sweeps and "mule-spinners" develop cancer of the scrotum owing to carcinogenic substances which saturate the trousers. Internal organs may also be affected, as in the case of aniline dyes, which are ingested or inhaled and are excreted in the urine, producing cancer of the bladder.

These facts serve to explain the existence of what has been called *social cancer*. It is evident that the incidence of cancer in the parts mentioned (including the lip cancer of fishermen) will be higher in members of the working classes. The upper part of the digestive tract must be included in this group. Some years ago the male population in England was divided into 5 social classes, and it was found that in the organs exposed to the exogenous carcinogens, including the digestive tract from the mouth to the pylorus, the cancer incidence was highest in the lowest social class and fell with a regular diminution through the other social classes to reach the lowest incidence in the highest social class. In the case of other organs, including the lower digestive tract, there was no relation of cancer incidence to social status. (Fig. 119.)



FIG. 119.—Cancer mortality by social classes. (Registrar-General's Decennial Suppl. England and Wales, 1921.)

The high incidence of gastric cancer may be due to chemical or mechanical insults or to defective oral hygiene.

Cancer of the stomach in man is extremely common, but cancer of the stomach in animals is remarkably rare. In 1913 Fibiger was awarded the Nobel prize for having succeeded in producing gastric cancer in rats by infecting them with a nematode worm subsequently named *Spiroptera neoplastica*; infestation was accomplished by feed-

ing the rats with cockroaches which were the intermediate host of the worm. This was an epoch-making achievement, for it was the first time that cancer had been produced at will in an experimental animal. Unfortunately it was shown some twenty years later that the lesions supposedly produced by the worm, namely, squamous metaplasia of epithelium and formation of papillomata, were in reality due solely to vitamin A deficient diet of white bread fed to the rats, that the cockroaches and worms played no part in the process, and that the lesions were not true examples of malignancy (Passey, Leese and Knox).

*Nutritional deficiency* may prove to be a carcinogenic factor in some instances. Copeland and Salmon kept rats for prolonged periods on a choline-deficient diet. Of these animals no fewer than 58 per cent developed some type of malignant tumor. In 40 per cent of animals

there was carcinoma of the liver, in 38 per cent carcinoma of the lung, whilst still others developed sarcoma and hemangioendothelioma. Here, as in the case of the chemical carcinogens, the primary change appears to be degeneration, followed by cellular regeneration and hyperplasia which passes into neoplasia.

*Trauma* is often accused of being an exogenous carcinogenic agent, nearly always (perhaps always) falsely. No tumor has ever been produced experimentally by a single trauma, even in animals with a high cancer incidence. Sarcoma of bone is often traced back to an antecedent trauma, but if such a causal relationship exists it is strange that the innumerable fractures of bone are never followed by sarcoma. In compensation cases a true history of trauma preceding the appearance of a tumor is often forthcoming. This can be explained in two ways. (1) The trauma, by causing pain and bruising, draws attention to the presence of a tumor (in the breast, etc.) previously unnoticed. Hemorrhage into the tumor may cause it to swell quickly, and this may be followed by more rapid growth. (2) Coincidence, seeing that both injury and tumors are so common. The possibility that a traumatic lesion can form the starting point of cancer cannot be denied. Special monographs have been devoted to this difficult subject.

Experimental evidence, however, suggests that trauma may act in conjunction with a carcinogenic agent. Thus tumors have occurred in healed or healing wounds in mice undergoing tar painting; this is known as the *Deelman phenomenon*. When deep excisions of skin are made in areas treated with benzpyrene, both benign and malignant tumors may develop (MacKenzie and Rous, Pullinger). In one case which came under my notice a patient with Paget's disease of bone sustained a severe injury to the right shoulder, which was followed in the course of a few months by the development of bone sarcoma at the site of injury. Patients suffering from Paget's disease have a marked tendency to develop bone sarcoma. There is on record the case of two identical twins, one of whom was struck on the left testicle by a plank; this was followed by the development of a malignant tumor of the testicle. A few years later the other twin developed a similar type of tumor also in the left testicle. In this and other instances it is possible that trauma and predisposition may act in conjunction.

**Endogenous Carcinogenic Agents.**—At first sight there may appear to be no connection between the exogenous and the endogenous factors. But a structural correlation exists between the chemical carcinogenic hydrocarbons and the sterol group of natural products. There seems to be an inherent tendency for the sterol molecule to pass into the cholanthrene ring system. While the work on the carcinogenic hydrocarbons was going on, organic chemists were investigating bile acids, the sterols such as cholesterol, and the sex hormones, and soon it became evident that the basic structure of these very different substances was fundamentally similar. All of them possess the condensed-carbon-ring skeleton known as the phenanthrene nucleus, and this nucleus is also present in the benzpyrene, benzanthracene and cholanthrene groups of

carcinogenic hydrocarbons. We have already seen that methylcholanthrene, which from its structure is seen to belong to the sterols, can be produced from bile acid by a series of processes which might well occur in the body. It becomes evident, then, that there is a structural relationship between the chemical carcinogenic compounds and the normal constituents of the body, and we must admit that it is theoretically possible for carcinogenic agents to be produced within the body as the result of disordered metabolism affecting the sterols, bile acids or sex hormones.

It appears probable that human organs may contain carcinogenic substances. Thus extracts of human liver when injected into mice produce malignant tumors in a small percentage of cases (Kleinenberg *et al.*). This percentage is much increased if the liver extract is made from patients dying of cancer. It is of interest to note that liver extracts of native Bantus when painted on the skin of mice produced benign and malignant growths, whereas no tumors were produced by non-cancerous European liver extracts (Des Ligneris). The latter work is based on the fact that the Bantu natives show a high incidence of primary carcinoma of the liver.

As the *sex hormones* bear a close structural resemblance to the carcinogenic hydrocarbons it might be deduced that their physiological activities are also similar. Such indeed proves to be the case. Certain of the hydrocarbons such as benzpyrene are able to replace the female sex hormone, whilst the administration of estrin may result in cancer. Thus carcinogenic substances can be estrogenic, and estrogenic substances can be carcinogenic. Estrin does not act locally on the skin or subcutaneous tissue like the carcinogenic hydrocarbons; it acts on the mammary epithelium which is normally under the influence of ovarian stimulation. Lacassagne has shown that if estrin is injected from birth onwards into a strain of mice which have a natural tendency to develop mammary cancer, the incidence of that tumor is very greatly increased, and even in male mice of the same strain mammary cancer can be produced, although the natural occurrence of this tumor in the male is almost unknown. Even when the hormone is painted on the skin it produces its characteristic effect on the breast. It is important to note that if mice of a non-cancerous strain are used, the hormone is powerless to produce cancer. In this case, therefore, hereditary influence is more potent than hormonal influence. Removal of the ovaries at an early age in mice of a high cancer strain will prevent the occurrence of spontaneous mammary cancer, but administration of estrin will cause cancer to develop. Carcinoma of the cervix has also been produced by the prolonged administration of estrin.

The so-called *organizers* of the experimental embryologist are related in chemical structure to the sex hormones and the chemical carcinogens. Although the organizer is concentrated in one particular area, it exists in masked form in all parts of the embryo, probably in combination with a specific protein, and the occurrence of the type of tumor known as the teratoma may be due to this combination being



broken down (see page 313). It is possible that a masked carcinogen becomes similarly liberated under abnormal conditions of metabolism. For further information on the subject of organizers in relation to carcinogenesis the reader is referred to Needham's book, *Biochemistry and Morphogenesis*.

**The Exciting Cause.**—We have already seen that carcinogenic agents, in spite of their name, do not actually produce cancer; they induce a state (precancerous state) in which cancer suddenly develops. At this stage, as Cramer puts it, the scene changes from the exterior to the interior of the cell. The precancerous stage affects a large area, as in tarring of the skin, but the irreversible intracellular change which constitutes malignancy usually involves only a few cells, although in some cases, as in cancer of the human skin, several separate foci of origin may be observed. As regards the preparatory cause or causes (carcinogenic agents) cancer is many diseases, but in respect to the immediate cause (the biological change in a cell when it becomes malignant) cancer seems to be a single disease. There are many methods of starting a fire, but the spread and maintenance of the fire is due to the liberation of potential energy locked up in the constitution of the inflammable material. There is a difference between starting and continuing. The fire continues when the remote cause has been removed, and the same is true of cancer. In this respect cancer differs sharply from bacterial disease, in which recovery follows removal of the infective agent.

Almost nothing definite is known about the immediate cause or the mechanism responsible for perpetuation of the process. Two possible factors deserve consideration, intracellular enzymes and filterable viruses. In relation to *enzymes* the work on the production of carcinoma of the liver by dimethylaminoazobenzene, the benzene-like dye known as butter yellow because of its color, is of special interest. When this dye is given by mouth to rats fed on a diet of rice and a little carrot, liver cancer regularly develops (Sasaki and Yoshida). If, however, yeast or liver powder is added to the rice diet, no cancer occurs, (Sugiura and Rhoads). These substances are rich in those vitamins of the B complex which are active in enzyme systems that carry on intracellular oxidation. This is the first instance in which experimental cancer has been prevented by a dietary constituent. The protective agents proved to be casein and riboflavin. Rhoads and his co-workers found that the administration of butter yellow caused a sharp fall in the amount of certain enzymes in the liver cells, whereas this fall was entirely prevented by the inclusion of yeast in the diet. The deficiency was due not to a lack of vitamin but to inability of the vitamin to function. Rhoads suggests that normal cell reproduction depends on the operation of enzymes which are conjugated proteins, *i. e.*, a protein linked with a vitamin, and that a carcinogenic chemical may take the place of the vitamin, the abnormal enzyme leading to the production of abnormal cells (cancer), whose descendants are also abnormal, and are beyond the control

forces which normally limit growth. It is thus possible that cancer cells may develop by a process of adaptation to an unfavorable environment, and in this connection it is worthy of note that malignancy is often preceded by degenerative and destructive processes followed by cellular regeneration.

Cancer cells sometimes seem to have the power of liberating substances like enzymes which can incite continuous growth, causing normal cells to assume the properties of malignant cells. In some cancers, as in carcinoma of the bowel, one can almost see this process going on under one's eyes, for the cells lining one part of a gland may appear normal whilst the adjoining cells may be frankly malignant.

*Filterable viruses* have for long been regarded by some workers as an important factor in the causation of at least certain forms of cancer, and fresh evidence accumulates in support of this view. The virus may be regarded as a self-perpetuating principle contained within the cell but separable from it. In order to transfer a tumor from one animal to another, living tumor cells must be implanted into the second animal. In 1910, however, Peyton Rous made the revolutionary observation that if an emulsion of a certain fowl sarcoma was passed through a filter and the cell-free filtrate inoculated into another fowl, a new tumor was produced derived from the cells of the second bird, not merely a continuation of the tumor of the first bird. Although the tumor is a sarcoma it has been shown by means of tissue culture that the cell attacked by the Rous agent is the macrophage, and that the tumor arises by a malignant transformation of this cell. The filter-passing, self-perpetuating agent which is contained in cells and can be transmitted to other cells is generally regarded as a virus, but it is evident that it also has the properties of an enzyme. Similar agents have been found in many other connective tissue tumors of birds. Lucké has described an adenocarcinoma in the kidney of the frog, containing prominent intranuclear inclusions and apparently due to a virus. In 1933 Shope showed that a cutaneous papilloma (benign) in the western cotton-tail wild rabbit was caused by a virus. Inoculation of the virus into the domestic rabbit produced aggressive papillomas, which frequently became cancerous in a few months and set up metastases. It should be noted that the filterable agent which is readily obtained from the benign lesion in the cotton-tail rabbit can no longer be found in the malignant lesion of the domestic rabbit. It seems to be bound to the cell in some way. This may have some bearing on the fact that transmissible agents have not been found in the malignant tumors of man and other mammals. The transmissible agent of filterable tumors is labile in fresh tissue and stored filtrate, but when the tissue is dried rapidly the agent is singularly stable; in one tumor kept in the dry state, the agent was as active as ever at the end of twelve years.

Duran-Reynals in a series of papers has demonstrated the fact that the age of the animal at the time of inoculation profoundly influences the type of reaction produced by the Rous virus. Moreover when the

fowl virus is injected into ducks within one day of hatching and into turkeys within ten weeks of hatching malignant tumors develop. Antibodies to the virus develop in the adult bird, so that chicks may be protected against the Rous sarcoma virus by serum from adult chickens.

Epithelial virus diseases may be pustular or proliferative in type. The reaction may be the former in one animal and the latter in another kind of animal. In sheep-pox the skin lesions are exudative, whilst the visceral lesions are highly hyperplastic. The type of animal may determine whether the growth response is to be benign or malignant, as in the case of the Shope papilloma virus. The development of malignancy may be accelerated by painting the skin with a carcinogenic agent, or by the action of a hormone in the case of the Bittner milk virus which produces carcinoma of the breast in mice (see below).

Rous points out that carcinogenic viruses differ from chemical carcinogens in the following respects: (1) The viruses are specific in their action, each invariably producing one type of growth, *i. e.*, papilloma of the skin in the rabbit, adenocarcinoma of the kidney in the frog, fibrosarcoma in the fowl. No known chemical carcinogen produces only one kind of tumor, and some, indeed, are pancarcinogens. (2) Multiplication of the virus is coterminous with the growth of the tumor it produces, whereas the chemical carcinogen initiates the growth, but may then be removed without affecting the continued development of the tumor. The relationship of the virus to the tumor is therefore much more intimate than in the case of the chemical carcinogens. (3) The carcinogens produce tumors in a wide variety of animals, whereas the viruses only produce tumors in the species of animal from which they have originally been isolated. (4) Ordinary carcinogens bring about tissue conditions out of which tumors may arise, whereas the viruses initiate tumors as well as determining their character.

Experiments suggest that exogenous and endogenous factors may work together, cutting down the time needed for the production of cancer. This is not surprising. Rous has shown that if the skin of a rabbit is first tarred for one or two months, and the virus of the Shope papilloma is then injected intravenously, the process is speeded up to an incredible degree, and after the normal incubation period of the virus (about two weeks) a highly anaplastic carcinoma develops in a few days which kills the rabbit in two or three weeks.

**Susceptibility.**—The action of a carcinogenic agent, whether exogenous or endogenous, is not sufficient to produce cancer. There must also be susceptibility to the agent on the part of the tissues. In animals of mixed strains the action of carcinogens is not uniform; some develop cancer, others do not. The difference is much more pronounced in the case of inbred strains, *i. e.*, strains which are bred to accentuate a natural susceptibility or a natural resistance to cancer. Maude Slye and many others have shown that inbreeding can bring out not merely general susceptibility to cancer but also *organ susceptibility*. A race of mice can be bred all of which will die of cancer of the breast. It has been truly said that pure strains of animals of known

hereditary tendencies are as important for cancer research as pure chemicals are for the chemist. If the degree of susceptibility is not so extreme, it will be brought out by employing the appropriate carcinogen. The ease with which a tumor may be induced experimentally depends on the genetic make-up of the host. Susceptibility conditions the action of every carcinogenic agent, whether it is exogenous or endogenous in type, but susceptibility plays a much more important part in the case of an endogenous agent such as a hormone which is always present. When the agent is an exogenous one its presence or absence is of much greater importance than the genetic constitution of the animal.

To picture the basis of susceptibility to cancer is naturally supremely difficult, but Cramer and Horning suggest that in the case of mammary cancer in mice there is hormonal imbalance between the ovary and pituitary, and that this imbalance can be restored by the injection of the thyrotropic hormone of the anterior pituitary with prevention of the cancer. They also observed that when estrin is used experimentally to produce cancer of the breast it affects the entire endocrine system, causing hypertrophy of the anterior pituitary and islets of Langerhans, atrophy of the thyroid, and a peculiar "brown degeneration" of the adrenal. Of special interest is the fact that this brown degeneration was observed to occur spontaneously in a strain of mice with a high incidence of mammary cancer before the appearance of the cancer. In a family of rabbits with a high incidence of spontaneous mammary carcinoma Greene observed the same changes in the pituitary, adrenal and endometrium as were produced by long-continued administration of estrin. All this suggests, however vaguely, that "susceptibility" may have a structural basis in the endocrine system.

The work of Bittner and also of Little suggests that there may be some maternal influence above and beyond inherited susceptibility. Bittner found that when newborn mice of a high cancer strain were fostered with mothers of a low cancer strain the tumor incidence was greatly reduced. Conversely newborn mice of a low strain when fostered by mothers of a high strain showed an increased incidence of cancer. Apparently some influence is transmitted through the mother's milk which determines the incidence of breast carcinoma. There seems now to be no doubt that this influence is a filterable virus, and that once it invades the body, it can be transmitted to the offspring. This brings up the question of the possible danger of a woman with a family history of breast cancer nursing her babies.

*Heredit*y plays an important part in experimental work in the laboratory. The inherited state is an unstable cell system confined to one organ or tissue; this system may break down because of functional strain or an unfavorable environment. To apply the experimental results to man is a task of great difficulty for obvious reasons, but the feeling is growing that the genetic factor is of real importance in human cancer. The occurrence of "cancer families" has long been described in the literature. There are families in which cancer appears

in every generation; when resistant strains marry into the family the offspring develop cancer. Here the tendency to cancer is dominant, and in some families every member will die of the disease if he lives long enough. Records of so-called cancer families are to be found in the literature. Broca describes a family of 26 members in three generations of whom 16 died of cancer. In the family reported by Warthin and brought down to 1936 by Weller 41 persons developed cancer out of a population of 305. As only 174 have attained the age of twenty-five, the cancer incidence is 23.6 per cent in those reaching that age. It is of great interest to note that 26 of the cancers were in the gastrointestinal tract and 15 in the endometrium. From the practical standpoint it may be said that the occurrence of an occasional tumor or tumors of different types in a family is of little significance, but that the frequent occurrence of one type of tumor points to a strong hereditary cancer disposition.

*Age* may be considered in connection with susceptibility. Cancer is predominantly a disease of middle or old age, although some forms occur at a much earlier age. At least 50 per cent of the cases occur over the age of sixty years, although this age group forms only a small fraction of the total population. This is not due to senility of the cells, for cancer can be induced as readily in a young animal as in an old one. It seems to be due to the fact that under natural conditions the preliminary process of preparation occupies a long period. When this preparation is due to such an endogenous agent as the female sex hormone, it is obvious that the resulting cancer cannot be expected to occur in the young. Yet in families with a high natural incidence of breast cancer, the age of onset of that disease is much earlier than in the general population.

There is a group of malignant tumors which occur in early life or not at all. These tumors, which may be present at birth or develop in early infancy, appear to be of congenital origin, and are dependent on some error of development in the organ involved. They occur in the retina, kidney, adrenal, and central nervous system. None of these tumors (retinoblastoma, neuroblastoma, Wilms' tumor, etc.) resemble adult carcinoma; evidently the mechanism of carcinogenesis is different from that of adult tumors.

The theory of *cell rests* may be invoked to explain these congenital malignant tumors. Cohnheim originally suggested that misplaced groups of cells or "rests" may act as the starting point of a tumor, because such cells are in an abnormal environment. These embryonic displacements are quite common, but tumors rarely arise from them, and it is doubtful if the Cohnheim theory deserves the popularity it has so long enjoyed.

When one considers the multiplicity of carcinogenic agents it is easy to agree with Rous' remark that every animal possesses a myriad of potentialities for tumor formation, and only by good fortune do most human beings slip through life without the realization of a single one of them. If the individual chews betel nut in Siam, or warms

himself with a kangri in Kashmir, or paints luminous watch dials in the United States he may spring the trap which is already set for him.

**Immunity to Cancer.**—Many facts are known about resistance to cancer, but at present they are confusing and cannot be coördinated into a whole. It might be thought that if a person showed susceptibility to cancer by developing the disease in one organ, the same would happen in other organs. This is not the case. There may be multiple malignant tumors of the skin or the large intestine, but multiple malignancy in different organs is uncommon. This possibly explains how it is that the total incidence in both sexes and various countries remains the same, though the incidence in different organs may vary widely; a high incidence in one organ seems to balance a low incidence in another. Cancer of the alimentary tract in women is uncommon, whilst cancer of the reproductive organs is very common; in men the reverse is true. In Holland cancer of the breast and uterus is only one-half as common as in England, but gastro-intestinal cancer is much more common. In Japan cancer of the breast is rare and cancer of the uterus is common. The total incidence of cancer is about the same in all three countries. In animals immunity to cancer may be acquired as well as natural. An animal which has developed a tar cancer cannot develop another as the result of a secondary tarring even though the first tumor be removed; the tissues seem to have undergone some mysterious change. Nor can tar cancer be induced in an animal with spontaneous cancer; it also is immune. But tar cancer can be produced in an animal with a transplanted tumor, and a tumor can be transplanted into an animal with a tar cancer.

**Spontaneous Cure.**—Many cases have been reported in which a cancerous tumor has apparently undergone spontaneous cure. Most of these should be regarded with very grave suspicion. Unless biopsy has shown unequivocal cancer, the case is worthless. Occasionally, however, the evidence is so well attested that to reject it flatly appears to be unscientific. One such case is reported by Kellogg Speed. A young man suffered from an osteogenic sarcoma of the leg, which was amputated. Within ten months he developed pain in the chest, bloody sputum, and there was x-ray evidence of pulmonary metastases. The patient was perfectly well thirteen years later. Such a case would make the fortune of a quack cancer cure.

The occurrence of cancer in a person or animal appears to depend on the operation of the two factors, carcinogenic stimulus and susceptibility, to which may be added a third factor, time, which varies inversely with the strength of the stimulus and the degree of susceptibility. It is shortest when a powerful stimulus is applied to a very susceptible animal, and longest when the other two factors are weak. If the stimulus acts with sufficient intensity and duration it may act almost alone. On the other hand susceptibility may be so marked that neither stimulus nor time seem to matter, as in the family described by Leschcztner where a mother and three daughters died of

cancer of the breast at the ages of twenty-two, twenty-one, nineteen, and fourteen years respectively.

To sum up this discussion of carcinogenesis, using the term in its wide sense as including both experimental and human cancer, there are three main factors: the carcinogenic agent (exogenous or hormonal), susceptibility (determined by heredity), and the time factor. Cancer can arise when the susceptibility is high and the carcinogenic stimulus is weak, or when the susceptibility is low and the carcinogenic stimulus is strong. The time period is shortest when the susceptibility is high and the stimulus is strong; it is prolonged when both factors have low values. It follows that when cancer appears at an early age both factors have high values; when it appears late in life both factors have correspondingly low values. For a discussion of these and many other related subjects the reader is recommended to study Cramer's excellent paper published in 1942.

**Transplantation of Tumors.**—All the earlier experimental work on tumors dealt with the transplantation of a spontaneous tumor from one animal to another. This was before tumors could be produced at will. The mouse was chiefly used, as it often suffers from spontaneous cancer of various types. In the past it has only been possible to transplant a tumor to another member of the same species, and because of this strict specificity it was not possible to work with human material. Greene has overcome this difficulty by employing the anterior chamber of the eye, and has succeeded in transferring human cancer to rabbits and guinea-pigs. This has made it possible to bring human cancer within the range of experimental investigation. The new tumor is not composed of cells of the animal in which it grows but of the proliferated tumor cells of the animal from which it was originally taken. The host animal merely acts as a culture medium for the tumor cells of the original animal. By continued passage a tumor can be kept growing forever; like the germ plasm it is immortal.

**Is Cancer Increasing?**—This question, so often asked, is not easy to answer without giving a false impression. Undoubtedly there are many more deaths from cancer than there used to be. In Canada in 1901 the cancer death rate was 46.8 per 100,000; in 1921 it had risen to 75 per 100,000 an increase of 62 per cent. But in deciding whether the increase is real or apparent, such factors as the general age of the population have to be borne in mind. The larger the proportion of old people, the higher will the cancer rate be. The truth appears to be that cancer is increasing both actually and relatively because of the great saving of life in the early years. It may also be said that the cancer rate is an index of the public health organization of a country; cancer is the legacy of preventive medicine. In the Vision of Mirza Addison describes the masses of mankind crossing the bridge of life which spans the river of death and falling into the dark flood below. In the bridge there are many trapdoors—infantile mortality, typhoid, malaria, smallpox—through which the unwary traveler may drop, but these seldom open now. So large numbers

approach the end of the bridge and drop through a small number of wide doors, such as apoplexy, coronary occlusion and, above all, cancer.

### THE EFFECT OF RADIATION ON TUMORS

No aspect of the study of tumors is of more practical importance than the effect of irradiation, whether by roentgen-rays or the gamma rays of radium. Only the general principles can be indicated here, but each kind of tumor and indeed tumors of each individual organ have to be studied separately. The chief methods used are: (1) external radiation (roentgen-rays and radium), (2) surface application (radium), and (3) interstitial radiation (radium). For widespread malignant processes such as lymphosarcoma and leukemia roentgen-rays provide the more practical method. The use of properly screened gamma rays avoids necrosis, but permits the specific selective action of the rays on the tumor cells. As Colwell remarks: "The aim of all modern radio-therapy is to eliminate this indiscriminate caustic action, and by adequate filtration and graduated exposure to administer such doses as shall have the maximum destructive effect upon the neoplastic cells with the minimum of danger to normal tissues." The effects of radiation depend partly on the action on the tumor cells, partly on the action on the tissues.

1. **Effect on the Tumor Cells.**—The effect may be studied in tissue culture or in the body. This effect is twofold: (1) arrest of cell activity, and (2) degeneration and destruction of cells. Actively growing and dividing cells are much more sensitive than ordinary cells. This is expressed in the "law of Bergonié and Tribondeau," that the radio-sensitiveness of any tissue depends on its reproductive activity. The more numerous are the mitoses, the more sensitive is the tissue. It follows that granulation tissue, embryonic tissue, and undifferentiated rapidly dividing cancers are most radio-sensitive. Partial or complete degeneration of the cell occurs. The nucleus breaks up and undergoes chromatolysis, the cytoplasm becomes granular and vacuolated, the cell dies and disappears. It has already been suggested (page 251) that radiation interferes with the metabolism of the nucleoproteins of the nuclear chromatin, upon the activity of which cell division is dependent. The name of Strangeways of Cambridge must always be associated with the work on tissue culture of tumors, and Canti has made moving pictures of the cellular response to radiation which for drama and thrill equal any product of Hollywood. Many of the cells die a sudden death, and can be seen on the screen actually to "explode." The degree of sensitiveness depends on the position of the cell in the mitotic cycle, the most sensitive period being just before the commencement of mitosis. All the cells in the culture are never killed, even though the dose largely exceeds the therapeutic limit, but the lethal effect is much greater than would at first sight appear. When subcultures are made of the irradiated culture it is found that the remaining cells have lost their power of reproduction,



although this loss may not become apparent until the culture has passed through a dozen generations. As a result of this delayed effect all the cells ultimately die.

Recent work shows that a primary effect of radiation on cells in tissue culture is a selective diminution in their respiration, while glycolysis remains constant. This interference with respiration is probably one of the chief modes of action of the rays. It is effected by action on the nuclear and cell membranes, by destruction of the mitochondria which are supposed to be concerned with cellular respiration, and by lack of oxygen supply due to vascular thrombosis. Thus the action of radiation on normal and neoplastic tissue is a complicated one, and not at all simple.

Two types of effect may be obtained, depending on the method used.

(1) *Autolytic degeneration* and softening. This is best seen in anaplastic undifferentiated tumors such as lymphosarcoma and Ewing's tumor of bone, but by using appropriate screening a similar effect may be produced in cancer of the mouth, tongue, tonsil, and cervix uteri. (2) *Growth restraint*. Resistant tumors such as osteogenic sarcoma of bone when radiated over a long period may cease to grow, though failing to disappear. They have become quiescent, their malignancy is greatly diminished, and they can then be removed surgically with greater safety.

2. **Effect on the Tissues.**—Radiation acts as an irritant and produces an inflammatory reaction in the stroma of the tumor and in the surrounding tissue. An exudate is formed consisting of serum and cells. The cells are at first polymorphonuclear leucocytes, but these are replaced by lymphocytes, plasma cells, and eosinophils. These cells appear to play some part in a defense reaction. The fibroblasts are stimulated to proliferate and lay down collagen fibrils, so that a dense fibrosis is the result. Perhaps the most important reaction is in the vessels. Both the bloodvessels and lymphatics show a marked obliterative endarteritis, with the result that the lumen is either greatly narrowed or completely occluded. Thrombosis is common. The result of these vascular changes is twofold. (1) The lack of blood supply leads to degeneration in the tumor, and some of the cellular changes are due to ischemia rather than to the direct action of the rays. (2) The lymphatics and blood channels being closed, embolism is not liable to occur, so that the surgeon may safely postpone operating while irradiation is being carried out, and when the tumor is removed there is less chance of embolic spread of cancer cells.

The part played by the tissue reaction explains some of the difficulties encountered in treatment. A cancer may be radio-sensitive, but when it invades bone it becomes radio-resistant. Rodent ulcer is a good example of this. The interstitial reaction is not able to take place in the non-vascular dense bone. Cancer of the breast responds rather poorly to radiation, because the breast is so rich in fat, and this tissue with its limited blood supply seldom shows a marked reaction.

**Radio-sensitivity.**—The sensitivity or resistance of a tumor to radiation depends on a number of factors.

1. *Differentiation.*—The more differentiated the cells and adult the type of tissue, the more radio-resistant is the tumor. Grade 1 epidermoid carcinoma is an example. Innocent tumors are radio-resistant. Of course, this term is only relative. Growth restraint will occur even in an innocent tumor. Myoma of the uterus (fibroid) is an exception, for it reacts to radiation with liquefaction. The anaplastic and undifferentiated highly cellular tumors, especially those showing many mitoses, are highly sensitive. To this there are important exceptions. Glioblastoma multiforme (a form of glioma), melanoma and neurogenic sarcoma may be very anaplastic and highly malignant, yet they are very radio-resistant. On the other hand, a slowly-growing tumor such as rodent ulcer with very few mitotic figures responds readily to radiation. By the method of micro-incineration it can be shown that the degree of radio-sensitivity of a malignant tumor depends on the inorganic ash content, *i. e.*, on the amount of inorganic material in the nucleus (Cathie). A careful distinction must be drawn between sensitivity and curability. Some of the most highly malignant are the most sensitive and the local tumor rapidly disappears, but extension of the tumor has already occurred and the patient dies of distant metastases. Examples are lymphosarcoma, highly anaplastic carcinoma (Grade 4), Ewing's tumor of bone. This is the radiological counterpart of "the operation was successful but the patient died." In a mixed tumor of the testicle (teratoma), consisting partly of embryonal and partly of adult tissue, the former is destroyed by radiation and the latter is unaffected, so that the tumor though biologically altered may not change in size.

2. *Stroma.*—If the stroma is dense as in cartilage and bone, radiation has little effect. Osteogenic sarcoma of bone with its abundant stroma is very radio-resistant. Long-continued radiation, however, appears to lessen the likelihood of metastases. Ewing's tumor of bone and all the other highly radio-sensitive tumors have a minimum of stroma.

3. *Nature of the Tumor Bed.*—Reference has already been made to the fact that when cancer cells invade bone or fat they become more resistant or at least more inaccessible.

4. *Infection.*—Infection bears a very important relation to radio-therapy. When tumors become infected they become more radio-resistant. At the same time interstitial radiation breaks down the resistance of the tissues to infection. The result is that unless infection of such a tumor as carcinoma of the rectum is reduced to a minimum by a preliminary colostomy, the effect of interstitial radiation on the tumor may be disastrous.

5. *Acquired Resistance.*—If repeated inadequate doses of radiation are used the tumor becomes more radio-resistant. Adequate dosage is essential.

Malignant tumors may be divided according to their radiosensitivity

into three main groups: (1) highly radiosensitive: lymphosarcoma, multiple myeloma, lymphoepithelioma (transitional-cell carcinoma), embryonal carcinoma; (2) moderately radiosensitive: epidermoid carcinoma, carcinoma simplex, depending in each case on the degree of anaplasia; (3) highly radioresistant: fibrosarcoma, osteosarcoma, neurosarcoma, melanoma, glioma, adenocarcinoma (except adenocarcinoma of the thyroid).

It is important to bear in mind that the microscopic structure of a tumor is only one of a group of features which determine its radio-sensitivity. In many tumors the nature of the tissue of origin outweighs all other factors. Thus tumors of blood-forming tissues are sensitive, *e. g.*, lymphosarcoma, multiple myeloma, endothelioma, angioma, while tumors of the neutral crest cells are resistant, *e. g.*, glioma, neurogenic sarcoma, melanoma. Many tumors whose microscopic picture suggests that they are radio-sensitive show marked resistance. The gross character may be more important than the microscopic structure; thus malignant adenomas of the rectum and uterus can be destroyed by radiation when they are papillary in type, but not when they are infiltrating. The following clinical features may be much better guides to radio-sensitivity than the microscopic structure: the anatomical site; the extent of the disease (especially regional metastases); the extent of infiltration; the gross character of the tumor; the condition of the patient (one who is obviously sick as the result of the malignancy seldom does well under radiation).

### THE CLASSIFICATION OF TUMORS

Much has been written regarding the classification of tumors and many classifications have been suggested. The most useful working method is to try to determine the tissue, the type cell, from which the tumor arises. This way may be easy or it may be difficult or impossible. The most undifferentiated and anaplastic the tumor, the more difficult is it to recognize the type cell. In the description of the various forms of tumors some will only be referred to; these are more conveniently considered in connection with the organs from which they grow.

The classification to be used is as follows:

1. Connective-tissue tumors
 

	{	Fibroma
	{	Lipoma
A. Innocent	{	Myxoma
	{	Chondroma
	{	Osteoma
B. Malignant	{	Sarcoma
	{	Chordoma
2. Muscle-tissue tumors
 

	{	Leiomyoma
	{	Rhabdomyoma
3. Angioma
 

{	Hemangioma
{	Lymphangioma

4. Endothelioma
5. Tumors of hemopoietic tissues
  - A. Benign lymphoma
  - B. Malignant lymphoma
 

{	Lymphosarcoma Hodgkin's disease Leukemia Multiple myeloma
---	--
6. Pigmented tumors
 

{	Nævus Melanoma
---	-------------------
7. Nervous-tissue tumors
 

{	Glioma Neuroblastoma Retinoblastoma Ganglioneuroma
---	---
8. Epithelial tumors
  - A. Innocent
 

{	Papilloma Adenoma
---	----------------------
  - B. Malignant Carcinoma
9. Special forms of epithelial tumors
 

{	Hypernephroma Chorionepithelioma Adamantinoma
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10. Teratomas

### CONNECTIVE-TISSUE TUMORS

#### INNOCENT CONNECTIVE-TISSUE TUMORS

**Fibroma.**—The type cell of the fibroma is the fibroblast. It is composed of fibrous tissue. The proportion of cells to collagen fibers varies greatly. *Hard* fibromas are acellular with abundant collagen. *Soft* fibromas are highly cellular. Of course, there are all grades. The more highly cellular the tumor, the nearer does it approach to malignancy. It might be thought that the fibroma would be a common tumor. On the contrary, it is quite rare in a pure form.

**Gross Appearance.**—The gross appearance is that of an encapsulated rounded tumor, firm, white in color, the cut surface being flat and intersected with glistening bands. *Microscopically* it presents intersecting bundles of fibers between which are a varying number of fusiform cells. (Fig. 120.)

**Sites.**—In the *skin* there may be hard or soft fibromas. As the latter arise from cutaneous nerves they will be considered in connection with neurofibromas. Fibromas of *mucous membranes* are found in the submucous coat of the stomach and intestines. They often project into the lumen and become pedunculated. *Visceral* fibromas occur in the ovary, kidney, and other organs, usually remaining quite small. Fibromas growing from the nasopharynx may attain a large size and threaten the life of the patient.

Fibroma of the *abdominal wall* is called a desmoid tumor (*desmos* band or fiber). It grows from the sheath of the rectus abdominis, and may attain a considerable size and invade the muscle. The muscle fibers enclosed in the tumor undergo a peculiar change with

the formation of multinucleated masses like foreign body giant cells. About 80 per cent of the cases occur in women who have borne children. In the remaining cases there is usually a history of trauma to the abdominal wall.

Fibroma of *nerve* may be divided into cutaneous neurofibroma and neurofibroma of the subcutaneous and deeper nerve trunks. (1) The *cutaneous neurofibroma* may be single, forming a firm and often very tender nodule in the skin. The tumor arises from the connective-tissue sheath of the nerve.



FIG. 120.—Fibroma showing fibroblasts and fibers.  $\times 400$ .

*Multiple neurofibromata* constitute the condition known as von Recklinghausen's disease, or molluscum fibrosum. There may be hundreds of tumors. They usually grow from cutaneous nerves and form soft nodules in the skin, but they may grow from the deep nerves and cranial nerves. The skin is often pigmented in patches. Death is not uncommonly due to sarcomatous change in one of the tumors.

(2) *Neurofibroma of the deeper nerves* grows from the subcutaneous nerves and the deeper trunks. It is much less common than the cutaneous form, but is of importance in that it has a strong tendency to become malignant. The condition is described more fully under the heading of Neurosarcoma or Neurogenic Sarcoma. A *plexiform neuroma* is a diffuse over-growth of the endoneurium of the nerves in the subcutaneous tissue. It is made up of coiled and thickened nerve trunks, many of which can be dissected out. The usual site is the head and neck.

A *keloid* or *cheloid* is not a true tumor but an excessive formation of scar tissue. It is a firm patch, raised above the surface of the skin, and it sends out claw-like processes as it grows. It is common in negroes, and some persons have an idiosyncrasy for the condition so that any scar may become hyperplastic. If it is excised it usually recurs.

*Xanthoma*.—As its name indicates, a xanthoma is a yellow tumor (*xanthos*, yellow), and has the general structure of a fibroma. At least three distinct forms can be distinguished.

1. *Xanthelasma*, by far the commonest variety, is not a real tumor but a degeneration of the muscle of the eyelid. It occurs as small yellow nodules on the eyelid in elderly persons.

2. *Xanthoma multiplex*, also known as *X. diabeticorum*, in which groups of yellow nodules are scattered over the surface of the body. It is associated with a high blood cholesterol (the yellow color is due to cholesterol), and is therefore found in diabetes and obstructive jaundice.

3. *Large xanthomas* are rare tumors which occur in connection with tendon sheaths, and which may resemble giant-cell tumors.

All of the tumors are of a bright yellow color. They consist of connective-tissue cells greatly distended with lipid droplets (cholesterol ester) so that the cell has a pale and foamy appearance. In addition to these "xanthoma cells" there are fibroblasts and foreign body giant cells. The latter are especially numerous in the single large tumors, and these tumors often contain much blood pigment. In some cases a striking feature is the so-called Touton giant cells, which are characterized by a remarkable ring of nuclei right around the periphery of the cell. They may be very numerous. I have not met with them in any other condition.

In some forms of xanthoma the basis of the condition may be a general disturbance of lipid metabolism associated with hypercholesterolemia. In others the defect may be intracellular, involving certain cells of the reticulo-endothelial system.

**Dermatofibroma.**—In spite of its name, this is not a true fibroma of the skin. It is a small, hard, non-encapsulated lesion of the corium, usually occurring on the extremities. It is composed of large, irregular, fusiform cells running in many directions and interlacing. It may be highly cellular, or may have abundant collagen and few cells. An important feature is the ill-defined margin with infiltration of the surrounding tissue, and it is easily mistaken for melanoma and neurofibroma. It may contain blood pigment, and by some workers it is regarded as a sclerosing hemangioma. The histological features are well shown in Stecker and Robinson's paper, which reports 60 cases.

**Lipoma.**—A lipoma is a tumor composed of fat. It is a common tumor, occurring mainly in the subcutaneous tissue of the neck, shoulders, back, and buttocks. Occasionally it grows from the mesenteric and retroperitoneal fat, and still more rarely from the submucous coat of the stomach and intestine where it may form a polypoid mass. The "diffuse lipoma" of the neck is not a neoplasm but a lipomatosis. A lipoma does not waste when the rest of the fat wastes in cachectic diseases.

A lipoma is a soft, circumscribed, lobulated, encapsulated tumor, easily shelled out. It is not attached to the deep fascia, but the overlying skin is often dimpled, owing to fibrous bands passing between it and the tumor. The lipoma is a very innocent tumor, but retroperitoneal and perirenal lipomas may rarely contain embryonic portions which grow rapidly and infiltrate. These tumors are called liposarcomas.

**Myxoma.**—A myxoma is a connective-tissue tumor with the structure of umbilical cord. It very rarely occurs as a pure tumor, but mucoid or myxomatous degeneration is common in connective-tissue tumors, both innocent and malignant. The appearance of myxomatous degeneration in what appears to be an innocent connective-tissue tumor is always suggestive of a malignant change. A definite sarcoma showing myxomatous tissue is called a *myxosarcoma*. The *microscopic* appearance is that of Wharton's jelly in the umbilical cord. Branched connective-tissue cells are scattered through a jelly-like or mucoid matrix. This material can be stained with mucicarmine.

**Chondroma.**—A chondroma is a tumor composed of cartilage. It is hard, bluish-gray in color, and translucent like normal hyaline cartilage. This, and the fact that it is well lobulated and so encapsulated that it is readily shelled out, make recognition easy. Microscopically it differs from normal hyaline cartilage in that the cells are arranged singly instead of in groups. (Fig. 121.) Being non-vascular it is very liable to myxomatous degeneration. It often becomes calcified. It grows from the ends of long bones in young persons, originating from the epiphyseal cartilage. When the bone stops growing, the tumor also ceases to grow and becomes calcified or ossified. These tumors also grow from the bones of the hands and feet, and from flat bones like the sternum and pelvis. The latter may attain a great size, and sarcomatous change is common.

Cartilage is found in developmental tumors (embryomas) of the testicle and in mixed tumors of the salivary glands. These should not be called chondromas. Multiple chondromas (multiple cartilaginous exostoses) will be considered in relation to diseases of bone.

**Osteoma.**—New formations of bone are common (callus of fractures, exostoses, etc.), but true osteomas, like true fibromas, are comparatively rare. The *cancellous osteoma* is made up of cancellous bone. It originates from the epiphyseal cartilage as a chondroma, and though converted into bone a cap of cartilage covers the growing tip. As the bone grows in length the tumor becomes separated from the epiphyseal line. A *subungual exostosis* is a cancellous osteoma which grows from the dorsal surface of the terminal phalanx of the big toe. It forces the nail up and causes much pain. A *compact osteoma*, also called an ivory exostosis because of its hardness, grows from the vault of the skull. It is a sessile tumor which may press on the brain or invade the orbit.

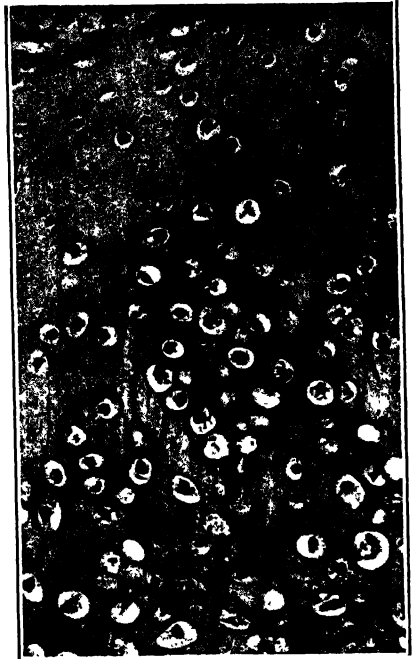


FIG. 121.—Chondroma.  $\times 240$ .

### MALIGNANT CONNECTIVE-TISSUE TUMORS

**Sarcoma.**—A sarcoma is a malignant tumor of connective tissue. It forms a large heterogeneous group, the limits of which should be greatly narrowed. Many tumors are called sarcoma although they

are not connective-tissue tumors nor do they behave like them. Such are lymphosarcomas, melanotic sarcoma, myosarcoma. None of these will be considered here, and where possible the names should be changed. Owing to long-established usage, this is not always possible.

The sarcoma group is being gradually limited. Chronic inflammatory conditions which used to be included are now regarded as granulomas. The same is true of certain forms of anaplastic carcinoma which may closely resemble sarcoma, *e. g.*, carcinoma of the testicle, ovary, and thyroid. It must be admitted that the microscopic differentiation of sarcoma on the one hand and chronic inflammation and anaplastic carcinoma on the other is often extremely difficult. The spindle-cell forms resemble granulation tissue, and the round-cell forms resemble anaplastic carcinoma. It is not always realized by the student commencing the study of pathology that carcinoma is an infinitely more common malignant tumor than sarcoma.

**Malignancy.**—The malignancy of sarcoma varies enormously. This adds to the difficulties of microscopic diagnosis. The more malignant forms are easily recognized as such, but as we approach the dividing line we encounter a picture which on the one hand may resemble a cellular fibroma and on the other hand granulation tissue. Only long experience will give the pathologist the feeling that a lesion is malignant, a feeling which he may find difficult to justify in words. With repeated removal of a recurring tumor the histological picture may alter markedly for the worse.

**Gross Appearance.**—The sarcomas vary so greatly that no general description can cover the group, but they have certain points in common. A typical sarcoma has a fleshy appearance (*sark*, flesh). It forms a bulky mass which is more sharply demarcated from the surrounding tissue than is a carcinoma. The more cellular forms may resemble the white matter of the brain. The tumor varies much in consistence, but it is often soft like the brain. The cut surface is homogeneous, and this is one of its chief characteristics. But degenerations are common, and these may interfere with the homogeneous character of the tumor. The growth of the tumor may outstrip its blood supply, with the result that a species of infarction occurs. Necrosis, mucoid or myxomatous softening, and actual liquefaction are frequent. The most common of these changes is hemorrhage from the abundant and very thin-walled bloodvessels.

**Microscopic Appearance.**—The less differentiated forms are highly cellular and the stroma may be so scanty as to be indistinguishable. The more differentiation, the more abundant and characteristic does the stroma become. Thus in the osteosarcoma there is osteoid tissue or bone between the cells. The general histological arrangement of a sarcoma differs fundamentally from that of a carcinoma in the same way that connective tissue differs from epithelium. The cells of a carcinoma are arranged in groups separated by a stroma, but the stroma does not penetrate between the individual cells of the group. This is called an alveolar arrangement, and resembles that of



the epithelium from which the tumor arises. In a sarcoma, on the other hand, there is no alveolar grouping; the cells are uniformly distributed, and are separated by a stroma. This may be very abundant as in bone sarcoma, or it may be so fine that it requires special staining methods to bring it out. Sarcoma cells have other mesoblastic characteristics. They tend to have poorly defined borders compared with carcinoma cells, and extensions of the cytoplasm form an intercellular matrix. Numerous blood vessels, often mere capillaries or sinusoids, penetrate the tumor, whereas in carcinoma the vessels are confined to the regular stroma which separates the groups of cells. Thus necrosis is more apt to occur in carcinoma, as the growth of cells outstrips that of the vessels. Sarcoma grows expansively on this vascular framework, and it is small wonder that hemorrhages are frequent. Carcinoma tends to grow rather by infiltration. Mitotic figures are significant in mesenchymal tumors, but much less so in epithelial tumors; they are often seen in inflamed and irritated epidermis.

The type cell may be the fibroblast, the osteoblast, the cartilage cell, etc. In the most undifferentiated forms the type cell cannot be recognized. We speak then of a round-cell sarcoma, spindle-cell sarcoma, etc. Many of these tumors are polymorphic, showing a variety of cells. Mitotic figures are very numerous in the rapidly growing sarcomas, scanty in the slowly growing ones. Their presence is of great value in the differentiation from a cellular fibroma, but it must be remembered that mitotic figures may be present in rapidly growing granulation tissue. Tumor giant cells form a feature of some highly malignant sarcomas. If the tumor becomes infected the giant cells may phagocytose many of the leucocytes, a rare occurrence. (Fig. 122.)

**Spread.**—A sarcoma grows *expansively* so as to form a bulky mass, but it also *infiltrates* the surrounding tissue. The rate of growth varies greatly. Unsuccessful (incomplete) operative interference is often followed by a great increase in the rate of growth. A rapidly growing sarcoma may sometimes outstrip its blood supply, so that the tumor may halt and even retrogress. At this stage it may react to roentgen-rays or potassium iodide by a reduction in size. Infiltration of the surrounding tissue occurs. The tumor cells creep along the fascial planes, between the muscle fibers, through the Haversian canals of bone, etc.



FIG. 122.—Phagocytic tumor giant cell.  
× 600.

Owing to this tendency removal is likely to be incomplete and recurrence is very common.

*Distant spread* takes place by the bloodvessels. The vessels are so abundant and so thin-walled, and the sarcoma cells so readily invade them that early blood dissemination is inevitable. Metastases are first formed in the lungs, but the tumor cells may pass through the lungs to any of the viscera. Owing to this early spread the lungs should be roentgen-rayed for metastases even in what appear to be the most operable of sarcomas. Spread by lymph stream is uncommon, but may occur in from 5 to 10 per cent of cases.

The *sites* of a sarcoma are varied, since connective tissue occurs in every part of the body. They are especially common in bone, subcutaneous tissue, fascia, and muscle.

Two methods may be used in the classification of the sarcoma. The first is cytological, the second histological. In the first the tissue is named according to the form of cell which predominates, so that we have a round-cell (small and large) sarcoma, a spindle-cell (small and large) sarcoma, a mixed-cell sarcoma, and a giant-cell sarcoma. This method is the refuge of the destitute, and should be avoided to the utmost of one's ability. In the second or histological method the tumor is named according to the type of connective tissue from which it arises, so that we have a fibrosarcoma, osteosarcoma, chondrosarcoma, etc. This is the only satisfactory method, but if differentiation has not gone sufficiently far it may not be possible. The interstitial tissue is often more characteristic than the cells of the tumor, *i. e.*, it may be osseous, cartilaginous, collagenous, etc.



FIG. 123.—Fibrosarcoma. The cells are large and fusiform.  $\times 1000$ .

**Histological Types of Sarcoma.**—1. *Fibrosarcoma*.—This is a spindle-cell sarcoma, the type cell being the fibroblast. (Fig. 123.) It is not really a common tumor, as used to be thought. Many malignant connective-tissue tumors formerly regarded as fibrosarcomas are now known to be neurogenic in origin, arising from peripheral nerves. The cells are fusiform, and may be small or large, the latter being the more malignant type. Both the gross and the microscopic features

vary much, depending on the degree of anaplasia. In the anaplastic forms the tumor may be very soft, and the cells may be so slightly fusiform that the non-committal name of round-cell sarcoma is applied. The stroma varies. It may be very scanty, or abundant fibrils may be formed so that it may be difficult to distinguish the tumor from a soft fibroma. The presence of mitotic figures is one of the most valuable points. Its behavior is that of a sarcoma of varying degrees of malignancy.

2. *Neurosarcoma (Neurogenic Sarcoma)*.—This is a tumor arising from the nerve sheath. It is a malignant form of neurofibroma. The tumor, which is not common and yet not rare, usually occurs in the subcutaneous and intermuscular tissue of the arm and leg. At first it is small and movable, and appears so innocent that it is excised under a local anesthetic with no attempt at wide removal. It reveals its true nature by promptly recurring. This may be repeated a number of times, until it is found that there are metastases in the lungs. In cases which are not touched growth may be slow and the tumor may remain localized for a long time.



FIG. 124.—Neurogenic sarcoma, showing the fasciculated arrangement.  $\times 300$ .

At first the neurogenic sarcoma is localized, but with continued growth and especially on recurring it infiltrates the surrounding tissue. The microscopic appearance is in general that of a fibrosarcoma, but the elongated cells are arranged in characteristic intertwining bundles, fasciculi and whorls. (Fig. 124.) This appearance suggests the neurogenic origin, but it may be very difficult to determine the question of malignancy. It is highly radio-resistant, a point of some value in differential diagnosis.

3. *Osteosarcoma (Osteogenic Sarcoma)*.—This is one of the most important and common forms of sarcoma. The type cell is the osteoblast, but it is by the intercellular substance (bone, cartilage) that it is most readily recognized. It is considered together with other bone tumors in Chapter XXXII.

4. *Chondrosarcoma*.—A chondroma may show evidence of malignancy (rapid growth, irregularity in the size and shape of the cells,

mitoses), and is then known as a chondrosarcoma. (Fig. 125.) It arises from a bone, often the sternum or pelvis, may attain a huge



FIG. 125.—Chondrosarcoma. Great irregularity in size of cells. Compare with Fig. 120, which has same magnification.  $\times 240$ .

size, and invades the bloodvessels causing pulmonary metastases. The distinction between a chondroma and chondrosarcoma may be very difficult, and the pathologist may have to depend on the clinical

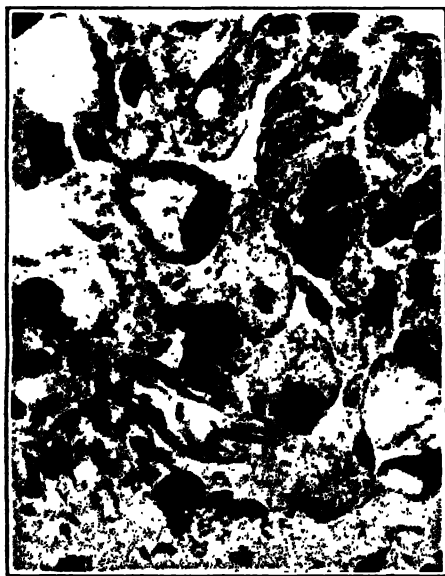


FIG. 126.—Liposarcoma. Some cells have granular cytoplasm, others are filled with fat.  $\times 510$ .

course and the gross appearance (invasion, etc.) rather than on the microscopic picture. Myxomatous degeneration should arouse suspicion.

5. *Liposarcoma*.—This tumor is by no means so rare as is commonly supposed; it is easily missed, especially if fat stains are not used. It

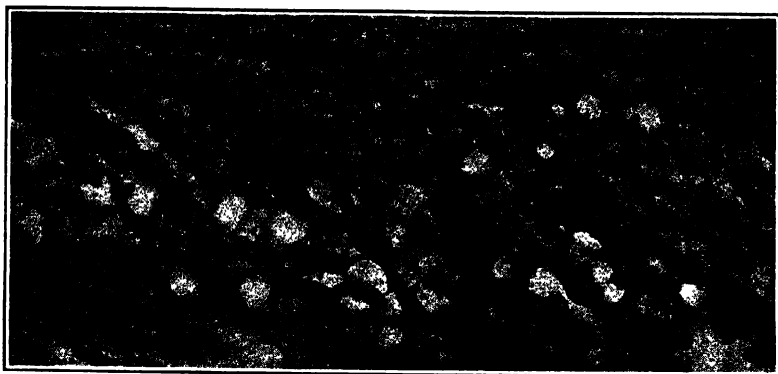


FIG. 127.—Myxosarcoma.  $\times 350$ .

may occur wherever there is fat, but is commonest in intermuscular tissue, around joints, and in the retroperitoneal and perirenal regions. At first encapsulated, it tends to recur after removal and then becomes infiltrating, so that the prognosis is bad. The microscopic picture varies in different cases, and there may be a most confusing variation in a single tumor. The common cells are spindle cells and large polyhedral cells; the cytoplasm is granular and may or may not contain fat, best shown, of course, by means of fat stains. The pale, swollen, polyhedral cells may resemble epithelial cells (Fig. 126) and thus suggest secondary renal carcinoma (hypernephroma), a mistake especially likely to occur when the tumor is in bone. Cells resembling fetal fat cells may be present, and tumor giant cells are not uncommon.

6. *Myxosarcoma*.—This is not a real group, but merely a mucoid or myxomatous degeneration of a sarcoma. (Fig. 127.) The term is useful if it serves to suggest the ominous character of myxomatous change in a connective-tissue tumor.



FIG. 128.—Chordoma. The clear vacuolated appearance of the cells is characteristic.

7. *Giant-cell Sarcoma*.—The name is misleading because the tumor does not behave like a sarcoma. It never (or almost never) gives rise to metastases. The tumor grows from the ends of the long bones and from the jaw under the gum. It will be described in the section on Bones under the title Giant-cell Tumor of Bone. A similar tumor occurs in relation to tendon sheaths.

**Chordoma.**—This tumor arises from remnants of the notochord, a structure of hypoblastic origin. It occurs at the upper and lower ends of the vertebral column, because the notochord is enclosed in the bodies of the permanent vertebrae. At the upper end it grows between the pituitary fossa and the foramen magnum, while at the lower end it occurs in the sacro-coccygeal region. It is a very rare tumor of rather low malignancy which spreads by infiltration, and only in the end stages does it form metastases. The tumor, which may reach a large size, is elastic in consistence, and shows numerous areas of translucent chordal tissue separated by patches of hemorrhage. *Microscopically* it consists of large clear cells closely packed together without any intercellular substance. The cells are distended with mucinous material, so that the tumor may be mistaken for a mucoid carcinoma. The cytoplasm, however, has a vacuolated appearance which is very characteristic. (Fig. 128.)

### MUSCLE-TISSUE TUMORS

Just as there are two types of muscle, plain and striated, so there are two forms of myoma or tumors arising from muscle cells. These are the leiomyoma and the rhabdomyoma. To these a third form, the myoblastoma, must be added.

**Leiomyoma.**—The leiomyoma (*leios*, smooth) is an innocent tumor of plain muscle. It is extremely common in the uterus, so much so as to constitute the commonest tumor in the body. It is known clinically as a "fibroid" because of its fibrous appearance in the gross, in addition to which much fibrous tissue may be interspersed with the muscle. The special characters of myomata of the uterus will be considered in connection with diseases of that organ. Their age incidence coincides with the period of reproductive activity. They never appear before puberty nor start to grow after the menopause. The uterine tumors are usually multiple and may be extremely numerous; evidently there are multicentric foci of origin. Leiomyomata are curiously rare in other parts of the body which contain plain muscle. They may occur in the ovary, tubes, and broad ligament, in the alimentary canal where they often form polypoid masses which project into the lumen, and in the bladder and ureters. The muscular walls of the bloodvessels are immune.

The *gross appearance* resembles that of a fibroma. The tumor may be of any size, from the very small to the very large. It is hard or at least firm, well encapsulated and easily removed. The cut surface presents a characteristically whorled appearance, due to interlacing bundles of fibers cut in various planes. Degenerative changes are common, such as hyaline and mucoid degeneration, softening, and sometimes complete calcification so that the tumor is converted into a mass of stone.

*Microscopically* the leiomyoma consists of interlacing bundles of plain muscle fibers, separated by a varying amount of fibrous tissue. The cells may be distinguished from those of a spindle-cell sarcoma by the long rod-like nuclei and the absence of mitoses. (Fig. 129.)

Occasionally a part of the tumor may become malignant, and is then called a *malignant myoma* or *leiomyosarcoma*. The nuclei are larger, the cells more active-looking, and mitotic figures can be seen. These

tumors seldom give rise to metastases, and may not recur after removal, so that they are usually not highly malignant.

**Rhabdomyoma.**—The rhabdomyoma is a tumor of striated muscle (*rhabdos*, a stripe). It is curiously rare, indeed extremely so. Nor is it found where it might be expected, *i. e.*, in voluntary muscle. A pure rhabdomyoma is the rarest of all, being practically confined to the heart. Striated muscle is found in embryonal tumors of the kidney, of the vagina of children, and of the testicle. In these tumors the muscle is mingled with other tissues. Only some of the cells are cross-striated. These mixed tumors are highly malignant and metastasize by the blood stream.

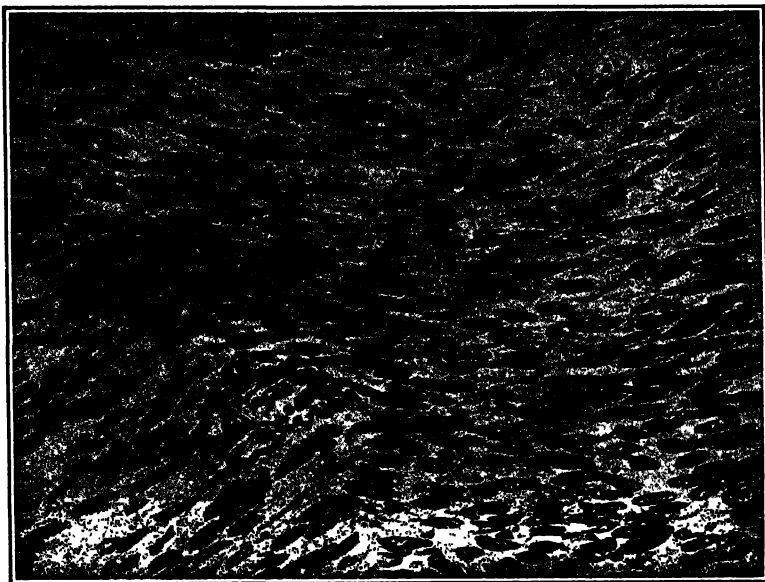


FIG. 129.—Leiomyoma showing plain muscle cells.  $\times 300$ .

**Myoblastoma.**—This tumor of striated muscle was first described in 1926, but 50 cases were reported in the next eight years. The common sites are the tongue, larynx and skin, but it has also been found in the lip, upper part of esophagus, and leg. It consists of polygonal cells with characteristic highly granular cytoplasm. In addition there may be ribbon-like syncytial masses with granular cytoplasm. No cross-striations are seen. It is open to doubt if these tumors really arise from primitive myoblasts, as is generally believed, for they may occur in sites devoid of striated muscle. Moreover they are essentially benign, whereas true differentiated rhabdomyoblastomas are highly malignant.

## ANGIOMA

An angioma is a tumor composed either of bloodvessels or lymphatics. The former is called a hemangioma, the latter a lymphangioma. The hemangioma is much the more common, and is commonly referred to as an angioma, the term lymphangioma being reserved for the lymphatic type.

**Hemangioma.**—A hemangioma is a new formation of bloodvessels. It may be difficult to distinguish this from telangiectasis, which is merely a dilatation of previously existing vessels. Two types are encountered, the capillary and the cavernous. The former is much the commoner.

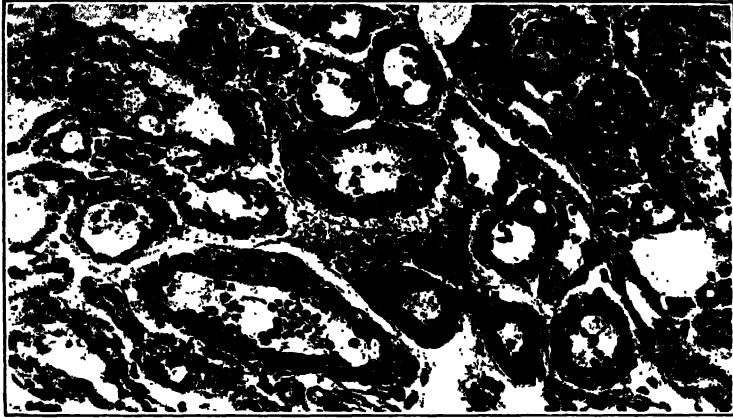


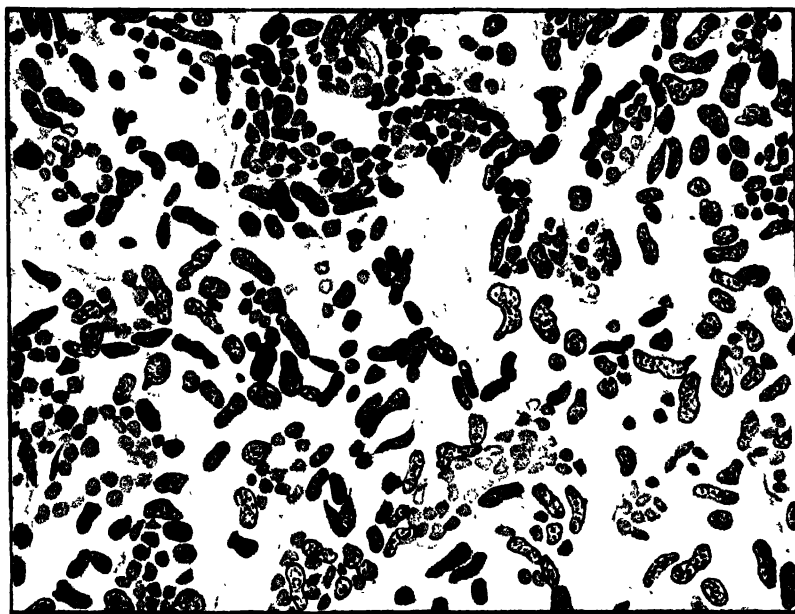
FIG. 130.—Capillary angioma. In addition to many new vessels there is a solid mass of endothelial cells in the upper right hand corner.  $\times 225$ .

**Capillary Angioma.**—This consists of a network of new-formed capillaries filled with blood. (Fig. 130.) The neoplasm affects only one segment of a vessel, from which buds of endothelium grow out and form new vessels. There is therefore a more or less closed system of vessels, not a dilatation of all the vessels of the part. The capillaries appear to arise from a rudiment destined to form bloodvessels, and thus form a mass which is to some extent withdrawn from the general circulation, so that any hemorrhage which may occur from it is not necessarily severe. Such a system may be obliterated by making use of the well-known action of radiation on vascular endothelium by which an obliterating endarteritis is produced. The endothelial cells are large and swollen and may be several layers in depth. (Plate VI.) Endothelial proliferation may be so marked that the lumen of the vessels is occluded, and solid masses of cells are formed. Such a condition is often called a *hemangio-endothelioma* or simply an endothelioma, for the tumor may appear to be solid and show little evidence of vascular lumen. The new-formed cells may have a whorled arrangement.

The common *site* is the skin, where the angioma forms a bright red, sharply-defined patch level with the surface. It is a congenital condition, usually present at birth, and it may extend so as to cover a large surface. The skin of the face and head is the usual site, but it may occur on any part of the body. On the face it often follows the distribution of the fifth cranial nerve and remains strictly unilateral.



## PLATE VI



Capillary Hemangioma

In addition to formation of new vessels there is marked proliferation of endothelial cells



These skin angiomas are known as port-wine stains, birth-marks, etc. They are often called *nævi*. The word *nævus* literally means birth-mark so that its use here is justified, but it seems better to reserve the term for another birth-mark, the pigmented mole, so as to avoid confusion. Capillary angiomas also occur in the mucous membranes of the nose, lip, tongue, gum and rectum, in all of which sites they may be a cause of troublesome hemorrhage. They form soft purplish-red patches which are easily recognized. In the tongue they are a common cause of macroglossia. Multiple angiomata may occur in the skin and the mucous membrane of the bowel, giving rise sometimes to intestinal hemorrhage. Angioma of bone is an uncommon but confusing condition, for it may present sheets of lipid-filled cells resembling those of a hypernephroma. As the lesion causes marked absorption of bone when seen in a roentgen-ray film, it is easy to make the mistaken diagnosis of secondary hypernephroma. Angioma of the brain constitutes one variety of cerebral tumor.

Certain hemangiomas exhibit regressive changes marked principally by fibrosis (Gross and Wolbach). In these *sclerosing hemangiomas* the capillaries become obliterated, whilst segregated groups of endothelial cells remain. In the majority of these cases there are accumulations of lipid material and hemosiderin which are probably extracted from the circulating blood (Gross and Wolbach), although to a lesser degree they may be derived from hemorrhages into the angioma. The lipid and to a lesser extent the hemosiderin are contained within phagocytic endothelial cells. Aggregations of endothelial cells may fuse to form foreign body giant cells. The tumors of the skin containing large amounts of blood pigment are often mistaken for melanomas. The granules of pigment are larger and more irregular in size and shape than the small, rounded and more uniform melanin granules. They are stained an intense blue by the Berlin blue method.

**Cavernous Angioma.**—This form is less common. It has the same structure as erectile tissue, being composed of large blood-spaces or sinusoids lined by endothelium. (Plate VII.) The commonest site is the liver, where it forms a small dark-red tumor which is discovered accidentally at autopsy. These tumors in the liver may be multiple, but they seldom become large. I have seen, however, a huge angioma which occupied the greater part of the left lobe of the liver. Being unrecognized it ruptured at operation, and the patient died on the table in the course of a few minutes. The cavernous angioma occurs in other positions, *e. g.*, lip, subcutaneous tissue, and muscle. It is not encapsulated, and may infiltrate the surrounding tissue like a malignant tumor. In rare cases metastases are formed in the lungs.

**Lymphangioma.**—This is much less common than a hemangioma. Like the hemangioma it is congenital. It may be localized or diffuse. The vessels may be small or cavernous, and they contain lymph instead of blood, so that the tumor lacks the characteristic color of the hemangioma. Lymphangioma of the tongue causes a diffuse enlargement, known as *macroglossia* (big tongue); a similar swelling of the lip is

*macrocheilia* (big lip). *Cystic hydroma* is a large soft swelling in the neck of children which may be mistaken for a cold abscess. More rarely it occurs in the axilla or the side of the thorax. It may be present at birth and tends to become smaller or disappear as the child grows up.

**Glomangioma Glomus Tumor.**—The word *glomus* means a conglomeration of minute arteries and veins. In the dermis of the extremities, particularly



Fig. 131.—Glomus tumor; glomus cells surrounding vascular channel.  $\times 225$ .

in the fingers and toes, there is an arteriovenous shunt by which the blood passes directly from the arteries into the veins without first passing through the capillaries. The channel along which the blood flows is lined by endothelium and surrounded by a mantle of large "epithelioid" or glomus cells; in addition there may be plain muscle fibers, while a rich plexus of non-medullated nerve fibers pass between the various cells. The epithelioid cells merge through a series of transitional forms with the typical spindle-shaped smooth muscle cells of the artery and vein. They appear to be derived from the pericytes of Zimmermann, specialized cells which are wrapped around the capillaries in all parts of the body and merge with the smooth muscle fibers (Murray and Stout). The entire mechanism constitutes a neuromyoarterial glomus, whose function appears to be to act as a kind of manometer controlling the circulation in the extremities and therefore the local temperature.

For the last one or two centuries the existence of "painful subcutaneous tubercles" in the extremities has been well recognized, but it was Masson who first in 1922 showed that these tumors arose from the glomus mechanism in the skin. Clinically these tumors are small, of slow growth, benign, confined to the extremities (common in the arm) and often situated under the finger nails, exquisitely tender, and characterized by paroxysms of burning pain during which the subungual lesions have a cyanotic appearance which is practically pathognomonic. Simple excision affords miraculous relief. *Microscopically* the tumor consists of a tangled mass of vessels surrounded by a fibrous capsule, and presenting the various elements (endothelial lining, glomus cells, plain muscle, and non-medullated nerve fibers) already described in the normal glomus. (Fig. 131.)

### ENDOTHELIOMA

The endothelial tumors form an ill-defined group regarding which there is great difference of opinion. One of the difficulties is to decide which normal structures should be regarded as endothelium, and another is to recognize endothelial cells under pathological conditions.

PLATE VII



**Cavernous Hemangioma**

The tumor is composed of large lakes of blood.



Endothelial cells stand midway between epithelial and connective-tissue cells. They produce an intercellular cement so that they are closely packed together, they grow in the form of cords and cylinders which may present lumina, and the nuclei are small and clear-cut, surrounded by a broad envelope of clear cytoplasm, compared with the large vesicular nuclei and granular cytoplasm of epithelial cells. A full discussion of this debatable subject would be out of place in a work of this size. It seems better to take up the various endothelial or supposed endothelial tumors as they are encountered. The angiomas are undoubtedly endothelial tumors and have already been considered. The reticulo-endothelium of the hemopoietic organs may give rise to tumors which are referred to in the next section. The malignant tumor of bone known as Ewing's tumor is considered by Ewing to be a form of endothelioma. Many endothelium-like tumors display sarcomatous characteristics, and it is hard to draw a sharp line of distinction. For a discussion of these and other matters the reader is referred to Ewing's great work, *Neoplastic Diseases*, where fifty pages are devoted to the subject of endothelioma.

#### TUMORS OF HEMOPOIETIC TISSUES, LYMPHOBLASTOMA

This group includes tumors of the lymphoid tissue and bone-marrow. The principal members of the group are lymphosarcoma, reticulum-cell sarcoma, Hodgkin's disease, leukemia, and multiple myeloma. Although these various conditions may be regarded as neoplastic diseases, it is possible that leukemia is not a true tumor, and probable that Hodgkin's disease is not. They arise in blood-forming organs, and will be considered in connection with diseases of these organs.

#### PIGMENTED TUMORS

No neoplasms have aroused more interest or excited greater differences of opinion than the group of pigmented tumors or melanomas. These tumors may be innocent or malignant. The former is sometimes called an innocent melanoma or *nævus*, the latter a malignant melanoma or melanotic sarcoma. In practice the innocent tumor is called a *nævus* and the malignant tumor a melanoma. The old term melanotic sarcoma should be dropped, for the tumor is not a sarcoma. The pigment is melanin.

**Nævus.**—The word *nævus* means a birth-mark and is applied to two different congenital lesions, the pigmented *nævus* and the skin angioma. These two conditions may conveniently be called a nerve *nævus* and a capillary *nævus*. It is better still to confine the term *nævus* to the present condition, calling the vascular lesion an angioma.

A *nævus* is a mole. It is usually pigmented, but may not be; the color varies from gray to brown or jet black. A mole is frequently covered with hairs and raised above the surface of the skin. It varies greatly in size, being usually quite small, but sometimes covering a large area of the body. A large *nævus* may show a "bathing-trunk"

distribution. Nævi are so common that nearly everyone has at least one tiny one, and the average person has over 20 pigmented moles. They are usually situated on the face, neck, or back, but they may occur anywhere. If they are raised above the surface and warty and are exposed to irritation from friction there is always a danger of their becoming malignant and they are better removed. Rarely a nævus occurs in the pigmented part of the eye (ciliary body, etc.).

A nævus is a congenital condition, but it may not be apparent at birth, and many pigmented moles do not appear until adult life. The great majority of nævi pursue an uneventful course; they may grow slowly for a time, remain quiescent for a long period, and gradually atrophy. A sudden increase in the rate of growth should at once arouse a suspicion of malignancy.

*Microscopic Appearance.*—A quiescent nævus consists of collections of clear, rounded or polyhedral cells in the dermis (corium), often

situated between downgrowths of epidermis. (Fig. 132.) These “nævus cells,” as they are called, are closely packed and present a very characteristic appearance. At the margin of the groups of nævus cells are more fusiform pigmented cells filled with melanin granules; these are melanoblasts, and give the lesion its color. The amount of pigment varies greatly, and bears no relation to possible malignancy. Gradually depigmentation of the nævus may occur.

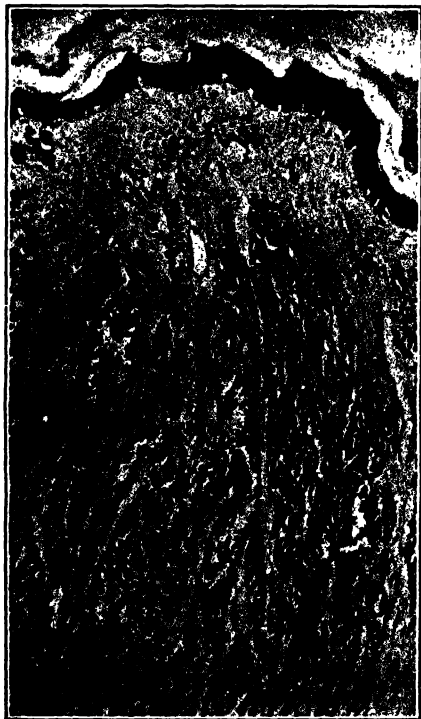


FIG. 132.—Nævus. The nævus cells are in the dermis and have no connection with the epidermis.  $\times 100$ .

**Histogenesis.**—An extraordinary difference of opinion has existed regarding the origin of the nævus cells. In turn, they have been regarded as epidermal (epithelial), mesoblastic, and endothelial in origin. A study of pathological tissue as well as the illustrations in Dawson's splendid monograph suggest that the cells have grown down from the epidermis, becoming isolated later. On the other hand, the chromatophores, which play so important a part in color changes

in the lower animals (chameleon, etc.), are mesoblastic in origin.

The older theories must be discarded in view of the work of Pierre Masson, who has shown conclusively that the nævus is of nervous



origin; the tumor is a neuronævus. The sensory nerves of the skin end in special sense organs. In the dermis the medullated nerve fibers terminate in Meissner's corpuscles, from which non-medullated fibers pass into the epidermis and end in the tactile corpuscles of Merkel-Ranvier. A nævus appears to be a proliferation of the entire end apparatus of the sensory nerves of the skin, in particular the cells of Meissner's corpuscles in the dermis. The type cell of the tumor is the cell of the tactile apparatus. With Masson's trichrome stain medullated and non-medullated nerve fibers can be demonstrated among the tumor cells. Even in sections stained by the ordinary methods the cells of a quiescent nævus may often be seen collected in definite end-organs of the type of Meissner's corpuscles in intimate relation to nerve bundles. In a series of specimens every transition can be seen from a normal end-organ up to characteristic groups of pure nævus cells. It would appear, therefore, that the nævus cell is neuro-ectodermal and not epithelial in origin.

The type cell may be non-pigmented and associated with nerve endings, or it may be pigmented and less intimately associated with the nerve endings. The former is the nævus cell, the latter the melanoblast, which has acquired the power of melanin production. The melanoblasts may form a mantle around the Meissner corpuscles, and are also regularly intercalated in the basal-cell layer of the epidermis, where they are known as Langerhans' cells. The degree to which the tumor is pigmented or non-pigmented depends on whether melanoblasts or nævus cells play a greater part in its formation. The wandering pigmented cells commonly seen in the dermis are histiocytes which have taken up the melanin formed by the melanoblasts; they may be regarded as mere carriers of pigment—melanophores or chromatophores (*phoreo*, I carry).

The *epidermis* also may take a part in the process of nævus formation, but the active cells are not epithelial but neuro-ectodermal in origin. Slumbering melanoblasts may be seen in the epidermis and also specialized cells like nævus cells in relation to the tactile corpuscles of Merkel-Ranvier. Thus the arrangement in the dermis is to some extent duplicated in the epidermis.

The neural origin of nævi would bring them into relation with neurofibromatosis (von Recklinghausen's disease). It is well known that pigmented patches of the skin are often seen in neurofibromatosis. Moreover in the more extensive forms of nævi such as the "bathing-trunk nævus" multiple neurofibromas may occur.

Laidlaw has brought forward an ingenious theory regarding the phylogenetic origin of the pigmented mole. He points out that these moles, which are essentially masses of cells in the corium containing sensory nerve endings, do not correspond with any structure in the normal mammalian skin, but that they do correspond with the tactile pigmented spots with which the skin of reptiles and amphibia is sprinkled. In the course of the ages the reptilian tactile spots are replaced by mammalian hair follicles, hair being primarily a tactile organ, although adapted secondarily to the functions of color and bodily warmth. The pigmented hairy mole appears to be a connecting link

between the pigmented tactile organ of the reptile and the hairy tactile organ of the mammal. It is reptilian in its pigment and groups of innervated tactile cells in the corium, but mammalian in its hair follicles. As Laidlaw puts it in his delightful paper: "In the reptilian tactile spot we find a full length portrait of the human pigmented mole, a pigmented elevation of the skin and a nerve coming up from below to innervate a group of tactile cells in the corium." The undoubted congenital character and frequent hereditary tendency of pigmented moles are in support of their phylogenetic origin.

**Malignant Melanoma.**—This tumor is commonly called melanoma or melanotic sarcoma. It arises in a *nævus* of the skin or in the pigmented coat of the eye. In the eye it is not preceded by an innocent lesion. About one-third of the cases of malignant melanoma arise in the eye. A mole exposed to long-continued irritation, friction, etc., is apt to become malignant. The frequency of *nævi* and melanomas is in proportion in most parts of the body, but melanomas are common on the feet (soles and under the nail) and on the genitalia, while *nævi* are quite rare, so that melanomas apparently do not arise from moles in these regions. Melanoma is a rare disease in the American negro, although common among the Sudanese; in the latter more than half the cases occur on the feet, which are exposed to puncture wounds from thorns, etc. In rare cases no lesion can be found in the skin or the eye, although secondary growths may have developed. In such cases the pia mater, the adrenal, and the intestine, especially the rectum, may be the site of the primary tumor. It must be borne in mind, however, that melanoma is an uncommon disease, while moles are extremely common.

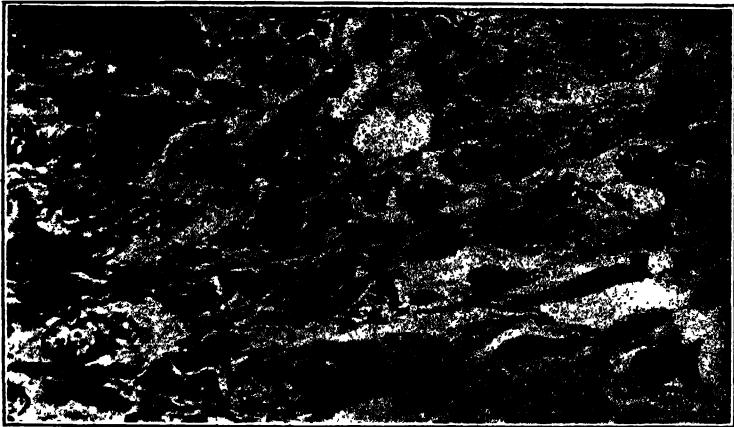


FIG. 133.—Malignant melanoma. Many of the large cells contain fine granules of pigment.  $\times 500$ .

**Structure.**—When a *nævus* is undergoing malignant change the tumor cells are seen to be extending into the deeper tissues. They have lost their quiescent appearance, and the cells are larger, the nuclei are hyperchromatic, and mitotic figures are present. (Fig. 133.) In a

fully formed melanoma the cells are large, polyhedral, and usually show a characteristic alveolar grouping, the groups being separated by a fine stroma. Such an arrangement gives the tumor a carcinomatous appearance. (Fig. 134.) In the eye, on the other hand, the arrangement is more likely to be sarcomatous and the cells fusiform, as in a fibrosarcoma. No tumor presents a more varied picture than the melanoma, and it is not too much to say that it may simulate a carcinoma, sarcoma, endothelioma, and even a lymphosarcoma. Pigmentation is usually marked, but this cannot be regarded as an invariable criterion, and the diagnosis may have to be made from the histological picture without the assistance of melanin. In non-pigmented

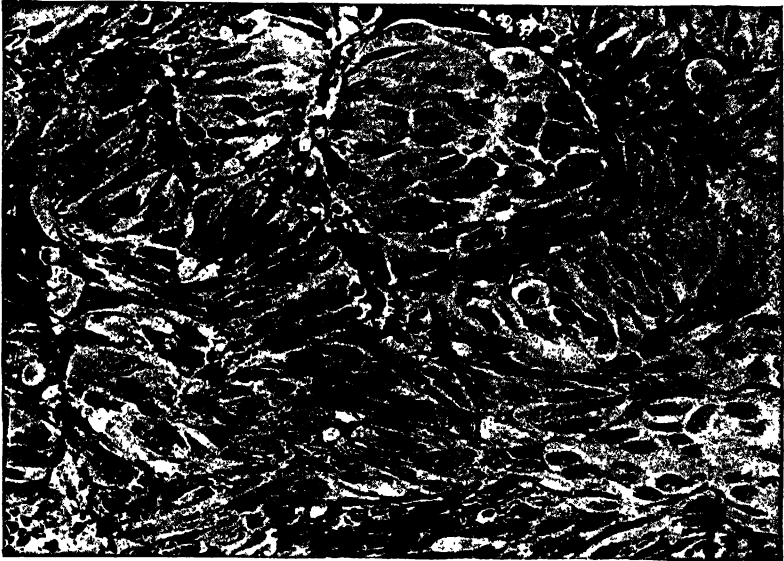


FIG. 134.—Malignant melanoma in skin showing characteristic acinar grouping of the cells, but no pigment.  $\times 275$ . (Boyd's Surgical Pathology, courtesy of W. B. Saunders Company.)

melanomas the dopa reaction (page 39) is of value, as it shows the presence of enzyme in cells which have not yet formed melanin. In one part of the tumor the cells may be loaded with pigment, while in another part they contain none. The pigment-bearing cells may break down and liberate the pigment, which is then taken up by phagocytic histiocytes. Although the tumor may be black to the naked eye the intracellular pigment is yellow.

**Spread.**—A melanoma is important not because of any local disturbance it produces, for usually it remains small; it kills by producing widespread metastases. The tumor cells spread by the lymphatics to the regional lymph nodes and by the blood stream to distant parts, although in melanoma of the eye there is no lymph spread. The

tumor spreads mainly and at first exclusively by the lymphatics; the regional lymph nodes soon become enlarged. Blood spread is a late event, and may be absent nearly until the end. When it does occur it is usually very wide, so that hardly an organ may escape. The skin is a common site of metastases. Secondary growths appear early in the skin; multiple growths of the skin even though non-pigmented should suggest a search for a primary melanoma. A history of loss of an eye from disease and an enlarged liver should suggest an ocular melanoma.

**Prognosis.**—The prognosis is grave, yet not necessarily so grave as is usually stated. The average duration of melanoma is from two to three years, but some cases remain localized for a long time, and even after the lymph nodes are involved removal of the primary tumor with the enlarged glands and the intervening lymphatics may be followed by cure. In the eye the outlook depends on the cellular type and on the amount of argyrophil fibers. When the tumor is of the spindle-cell type and silver-straining fibers are abundant, the prognosis is quite favorable.

### NERVOUS-TISSUE TUMORS

Although the central nervous system is ectodermal in origin, it becomes divided into parenchymatous tissue (nerve cells and fibers) and supporting tissue (neuroglia). Tumors of the parenchymatous tissue are very rare, tumors of the neuroglia are very common.

**Glioma.**—During recent years our knowledge of this important class of tumors has been greatly increased by the work of Bailey and Cushing. As a result of this work the gliomas can now be classified on a histogenetic basis, some of the groups differing widely from others in regard to prognosis. This work will be taken up in connection with Tumors of the Brain.

**Neuroblastoma.**—This is a tumor of primitive nerve cells or neuroblasts. It occurs not in the brain but in the medulla of the adrenal, which of course is neural in origin, and more rarely in connection with other parts of the sympathetic nervous system. It is practically confined to children under the age of four years. It is described in the section on Diseases of the Adrenal Glands.

**Retinoblastoma.**—This tumor has been called glioma of the retina, neuroblastoma, and neuro-epithelioma. It is composed of cells which started from the anlage of retina in the embryo and were not developed into functioning cells. It seems best, therefore, to use the term retinoblastoma. It is an uncommon tumor, and presents three striking clinical characteristics: (1) it is bilateral in at least 20 per cent of the cases; (2) over 90 per cent of the cases occur before the fourth year, in this resembling neuroblastoma of the adrenal; (3) it shows an extraordinary familial tendency. In a family of 16 children 10 died of retinoblastoma. The tumor is locally destructive, but later it may form metastases in the lymph nodes and internal organs. *Microscopically* it is composed of small round cells with practically no

cytoplasm and no fibrils. The chief characteristic is the presence of circles or "rosettes" of columnar cells, which, however, may be absent. They probably represent inclusions of cells which normally develop into rods and cones.

**Ganglioneuroma.**—A very rare tumor composed of adult nerve cells and fibers. (Fig. 135.) It is commoner in peripheral ganglia than in the central nervous system. The condition is benign.

### EPITHELIAL TUMORS

Epithelial tumors like epithelial cells present certain features which distinguish them from connective tissue cells and tumors. The cells lie in apposition with one another to form groups. The groups are separated from each other by connective tissue, giving what is called an alveolar arrangement, but there is no connective tissue between the cells of the alveolus. The innocent epithelial tumors are the papilloma and adenoma, the malignant is the carcinoma.



FIG. 135.—Ganglioneuroma.  $\times 300$ .

### INNOCENT EPITHELIAL TUMORS

**Papilloma.**—A papilloma is a benign epithelial tumor in which the cells cover finger-like processes of stroma. It grows from a surface, either internal or external. The term is usually not applied to malignant tumors when they grow in this way, but sometimes it is (malignant papilloma). A papilloma may become malignant, but this is only common in one or two situations, *e. g.*, bladder and rectum. Papillomata may be squamous or mucous, depending on whether they grow from a squamous or mucous surface.

**Squamous Papilloma.**—This tumor is commonest in the skin, (Fig. 136) but may occur in the mouth, larynx, and any other cavity lined by stratified epithelium. The base may be narrow or broad. Many conditions commonly called papillomas are not true neoplasms. The name *wart* is often applied to a papilloma of the skin, but the common warts of children (*verruca vulgaris*) which comes out in crops and disappear later are infectious in nature. Venereal warts (*condyloma acuminatum*) are also due to an infection. A skin *nævus* (mole) is often called a wart and may look like a papilloma.

A true papilloma shows proliferation of the squamous epithelium.

The epidermis may be thickened and blunt processes may project down into the corium. The so-called *plantar wart* is a flat papilloma with excessive epidermal thickening and very marked cornification of the surface layers. The thickened epithelium presses on the sensory nerve endings and causes pain on pressure just as does a corn. A corn is simply an excessive surface cornification. Every papilloma has a fibrous core, and in some cases there seems to be more overgrowth of fibrous tissue than of epithelium, which may be of normal thickness.



FIG. 136.—Squamous papilloma growing from skin.  $\times 7$ .

**Mucous Papilloma.**—This is commonest in the large intestine and bladder, but it may grow from any mucous membrane. In the stomach, intestine, etc., a papilloma is commonly called a polypus. Such a polypus is really more of an adenoma than a papilloma, for it is composed of proliferated glands. Gastro-intestinal polypi are often multiple, and in the large bowel there may be hundreds. Infection with *Bilharzia hæmatobia* may set up a papillomatosis both in the bladder and the rectum. Mucous polypi in the large intestine and bladder are of great importance because they show a marked tendency to malignant change. (Fig. 137.) The steps by which this transformation occurs have already been traced in discussing the relation of innocent to malignant tumors.

**Adenoma.**—An adenoma is an innocent epithelial tumor of glandular structure which closely approximates that of the gland from which it arises. Unfortunately the matter is not quite so simple as it sounds. Many so-called adenomas are not true tumors, but merely examples of localized compensatory hyperplasia. When a portion of the liver is destroyed a mass of new tissue is formed which may project on the surface and be mistaken for an adenoma. A true adenoma is encapsulated, but it is doubtful if the common encapsulated glandular nodules in the thyroid commonly called adenomas are really true tumors. Again an adenoma of the breast may contain more fibrous tissue than epithelium; such a tumor is a fibroadenoma rather than a pure adenoma.

No general description of an adenoma is possible. It is a circumscribed encapsulated nodule which may resemble the gland from which it arises so closely that the microscopic picture of the two may be



FIG. 137.—Mucous papilloma of large bowel. A malignant change had occurred in an adjacent part of the tumor.  $\times 60$ .



FIG. 138.—Adenoma of rectum. The new glandular acini are quite regular.  $\times 90$ .

identical. It consists of gland-like spaces (breast, stomach, bowel, pancreas), or solid cords (liver, adrenal). The glands may be lined by more than one layer of cells, but the acini are perfectly regular, and there is no invasion of the deeper tissue. (Fig. 138.)

In the stomach and large intestine the adenoma commonly develops a stalk owing to contractions of the muscular wall, so that it hangs into the lumen as a polypus. Such a polypus is often called a papilloma, but polypoid adenoma or adenomatous polypus is a more correct name. The frequent development of malignancy in the adenomas of the large bowel has already been alluded to.

The secretion of the cells lining the glandular spaces of an adenoma may lead to distention of these spaces with the formation of cysts. Such a condition is called a cystadenoma. It is best seen in the ovary, where the cysts are lined by tall columnar epithelium which secretes a mucoid material. The cells lining such cysts may become flattened from pressure, or they may proliferate and project as papillary processes into the cysts, a condition known as papillary cystadenoma.



FIG. 139.—Lymphatic permeation by carcinoma.  $\times 125$ .

## CARCINOMA

A carcinoma is a malignant epithelial tumor which tends to invade the lymph spaces of the surrounding connective tissue. It is the commonest of all malignant tumors, very much commoner than sarcoma. The cells show the characteristic epithelial arrangement; they are collected into groups or alveoli, with fibrous stroma between the groups but not between the cells of the group. The stroma varies greatly in amount, and largely determines the physical character of the tumor. When the primary tumor is sectioned it may appear to be made up of a large number

of separate masses. These are really extensions of the central mass which on section give a fictitious appearance of multiplicity. A wax model would reveal the essential continuity of the tumor.

**Spread.**—Carcinoma may extend in four different ways. (1) *Invasion of the tissue spaces.* This is the fundamental method of spread. The words cancer and carcinoma mean a crab, and these extensions are the claws of the animal. (2) *Lymphatic permeation.* The cancer cells invade the lymphatics and grow along them. (Fig. 139.) Spread



along perineural lymphatics is of importance in some tumors, particularly carcinoma of the prostate. (3) By *lymphatic embolism* tumor cells are carried to the regional lymph nodes and sometimes to more distant nodes. The nearer nodes may also be reached by permeation. (4) *Blood spread* carries the tumor cells to distant organs.



FIG. 140.—Glandular cancer in lymph node.  $\times 150$ .

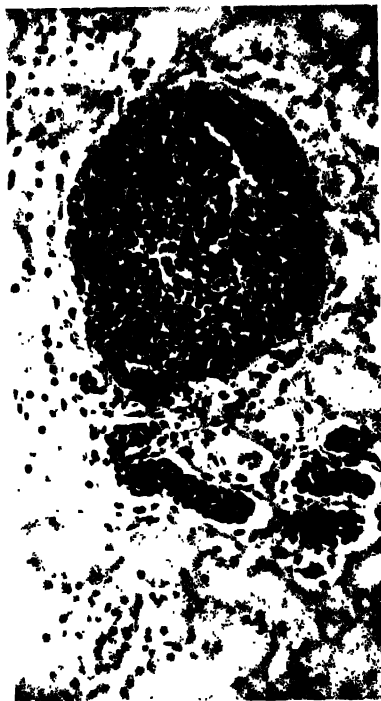


FIG. 141.—Metastasis from carcinoma of lung in glomerulus and renal tubules.  $\times 175$ .

Carcinoma spreads primarily by the lymph spaces and lymphatic vessels. Lymph node involvement is therefore the rule. (Fig. 140.) A lymph node may contain cancer cells and may yet appear normal to the naked eye and show no enlargement, a point of great surgical importance. Suspected early involvement of lymph nodes may be attacked by radiation. As the process becomes more advanced the gland is enlarged, and the cut surface shows a small opaque white nodule. Later the entire gland is occupied by the tumor. In that form of cancer known as squamous-cell or epidermoid carcinoma of the skin, tongue, etc., spread is almost entirely by the lymphatics, although in the last stages the bloodvessels may be invaded.

Spread by the blood stream is common, though not nearly so common as lymph spread. (Fig. 141.) In cancer of the gastro-intestinal

canal and pancreas the tumor emboli are carried by the portal vein to the liver to form metastases. In carcinoma of other organs (breast, etc.) the lung is the commonest seat of secondary growths. The bones are frequently the site of metastases in carcinoma of the prostate, breast, lung, kidney (hypernephroma) and thyroid. Skeletal metastases may occasionally occur from other carcinomas.

**Squamous-cell Carcinoma.**—This is usually called *epidermoid carcinoma* and used to be known as *epithelioma*. It occurs wherever squamous or transitional epithelium is found, particularly in skin, mouth, tongue, larynx, cervix uteri, and urinary bladder. Epidermoid carcinoma may develop in the edge of a chronic ulcer which refuses to heal. In rare cases it may arise from epithelium which has been changed from the columnar to the squamous stratified type owing to an irritation metaplasia. This is seen in the gall-bladder and in a bronchiectatic cavity in the lung. Most of the skin cancers are on the face and neck; the lower lip is the commonest site. They develop at a point where there has been chronic irritation (fissure, ulcer, local thickening). The tumor begins as a slight thickening or small nodule. At this stage the disease is easily curable. Later an ulcer forms which refuses to heal; the edges are characteristically thickened and indurated. Epidermoid carcinoma spreads by the lymphatics, so that the regional lymph nodes become infected and enlarged. They may be infected with tumor cells and yet show no enlargement. Blood spread is unusual, and only occurs late in the disease.

**Microscopic Appearance.**—Columns of epithelial cells grow down into the dermis. (Fig. 142.) The growth is therefore the reverse of that seen in papilloma. The lower parts of the columns often appear as masses separated from the rest of the growth by the obliquity of the section. In the center of these masses the same process of cornification goes on as occurs normally on the surface. Granules appear in the cytoplasm, and the cells become converted into hyaline structureless masses of keratin which stain brightly with eosin and are identical with the horny material on the surface of the skin. Such a general picture is well named an epidermoid carcinoma. The cornified masses are known as *cell nests* or *epithelial pearls*. The outer cells of the pearls are often arranged in a concentric manner. The unchanged cells show the "prickle-cell" appearance characteristic of epidermal carcinoma. Cell nests and cornification are absent in rapidly-growing tumors, as they are a sign of differentiation. They are best seen in skin cancers; sometimes they are found in cancer of the tongue and esophagus, but they seldom occur in cancer of the bladder or cancer of the cervix. The down-growing masses are often surrounded by masses of lymphocytes, especially in tumors of low grade.

The *grading of tumors* according to degree of malignancy is most easily done in the epidermoid carcinomas, because the signs of differentiation (prickle-cells, cell nests, cornification) are so distinctive. In Grade 1 all of these signs are well marked and there are few or no mitotic figures. The prognosis is excellent if the tumor is accessible

and can be removed. In Grade 4 there are no signs of differentiation, and the tumor may be so anaplastic that it may be difficult to be certain if it is an epidermoid cancer. Mitotic figures are numerous. The prognosis is bad or hopeless with surgical treatment, however early, because dissemination is widespread; radiation holds out much greater hope.



FIG. 142.—Epidermoid carcinoma. Epithelial down-growths into dermis and formation of cell nests.  $\times 60$ .

**Basal-cell Carcinoma.**—*Rodent Ulcer.*—This is a variety of squamous cell carcinoma which differs both clinically and pathologically from typical epidermoid cancer. It is relatively benign, of remarkably slow growth, and does not involve the regional lymph nodes. It presents the anomaly of a tumor which is relatively undifferentiated and is yet of low malignancy. Being undifferentiated it responds well to radiation, but not if it has infiltrated the underlying bone. The distribution is highly characteristic. The lesion occurs on the upper part of the face about the cheek, nose, eyelid, and ear, above a line drawn between the tip of the ear and the angle of the mouth. It is, however, by no means confined to this region, and may occasionally occur on other parts of the skin. Not infrequently rodent ulcers are multiple, the skin of an area (usually the face) developing a tumor-forming tendency. Exposure to bright sunlight appears to

be a causal factor. In Australia where the light is very strong and the humidity very low the disease is extremely common. As many as 50 cases a day may be seen in the out-patient department at Sydney. The conditions in Australia are peculiar, for it is a country with a tropical sun in which there is nothing but white labor. In other tropical countries those who are continually exposed to the brilliant glare have colored (protected) skins. It is interesting to note that the large Italian element in the labor population in Australia is relatively immune. The disease is much commoner at the north end of New Zealand than in the south. The tumor slowly erodes the deeper tissues, and in this way may cause great destruction of the nose, the contents of the orbit, etc. For this reason it is commonly called *rodent ulcer*.



FIG. 143.—Rodent ulcer. The basal-cell character of the growth is evident.  $\times 90$ .

The *microscopic appearance* is quite different from that of epidermoid carcinoma. It consists of solid masses of darkly-staining cells which extend down into the dermis, although often no connection with the epidermis may be seen in a given section. (Fig. 143.) The columns extend down to a uniform level, and their ends have an expanded club-shaped appearance. There is none of the eosin-staining so characteristic of epidermoid carcinoma, no cell nests, no cornification. The

cells are all of the same type as the basal cells of the epidermis and therefore stain blue with hematoxylin. There are usually no mitotic figures, but they may occur in the more rapidly-growing forms. Very occasionally there is a mixed picture of the basal and squamous forms.



FIG. 144.—Adenoid cystic epithelioma showing cystic spaces. Note the resemblance to rodent ulcer.  $\times 14$ .

Regarding the *origin* of the tumor there is difference of opinion. It is best to take the term "basal cell" to indicate that the tumor maintains the character of basal cells. There are three possible sites of origin: the basal cells of the epidermis, the hair follicles, and misplaced cell groups from the epidermis. Some of the tumors may arise in one way, some in another. The fact that they are often situated along the line of embryonal fissures on the face supports an origin from misplaced cell groups.

*Adenoid cystic epithelioma* (Brooke's tumor) is an uncommon form of squamous-cell carcinoma, but its recognition is important because of its comparative lack of malignancy. It occurs at a much earlier age than rodent ulcer, and forms a heaped-up lesion on the surface. It consists of epithelial masses showing both a glandular arrangement and cyst formation. (Fig. 144.) The latter is the most striking feature. The cells may be of the squamous- or the basal-cell types.

**Tumors of Sweat Glands.**—Closely related to the benign cystic epitheliomas are tumors of sweat glands. The tumor may be an adenoma arising from the alveoli, known as a *spiradenoma* (*speira*, a coil), and presenting a highly characteristic microscopic appearance of large numbers of sharply circumscribed masses of cuboidal cells. They are often multiple, and a common position is the scalp, where, on account of their multiplicity, they may form what is known as a "turban tumor." The ducts may be dilated to form cysts. Adenocarcinoma is much less common, and is of low malignancy.

**Lympho-epithelioma.**—A cancer of distinctive individuality, both clinical and pathological, grows from the epithelium covering lymphoid tissues in the mouth and pharynx, *i. e.*, tonsil, wall of pharynx, nasal passages, and nasopharyngeal sinuses, in which areas the epithelium tends to be transitional between squamous and simple. Its chief

characteristic is that the primary growth remains small and often undetected, whereas early dissemination gives rise to marked enlargement of the glands of the neck. The correct diagnosis of these nasopharyngeal tumors is often missed for a long time. Visceral involvement (lungs, liver) may occur at a later date. *Microscopically* the cells are large and pale with indefinite outlines, and are arranged in sheets. There is usually a marked intermingling of epithelial cells and lymphocytes derived from the underlying lymphoid tissue. (Fig. 145.) When the tumor is purely epithelial in type it is referred to as *transitional-cell carcinoma*. Mitoses are numerous. There may be a tendency toward differentiation with squamous characters appearing, or toward anaplasia so that the tumor in the lymph nodes may be

mistaken for a lymphosarcoma. The tumor is markedly radio-sensitive, in distinction to epidermoid carcinoma, and is more suitably treated by radiation than by surgery. In essence it is an anaplastic carcinoma of the throat.

**Adenocarcinoma.** — This is a columnar-cell carcinoma with formation of glandular spaces. The common sites are the stomach, large intestine, gall-bladder, pancreas, uterus, and prostate. It may occur in the breast and other glandular organs. Spread occurs both by the lymphatics and the blood stream. The gastro-intestinal tumors usually form bulky masses which project into the lumen, but they may be sessile or infiltrating. The change from the normal mucous mem-

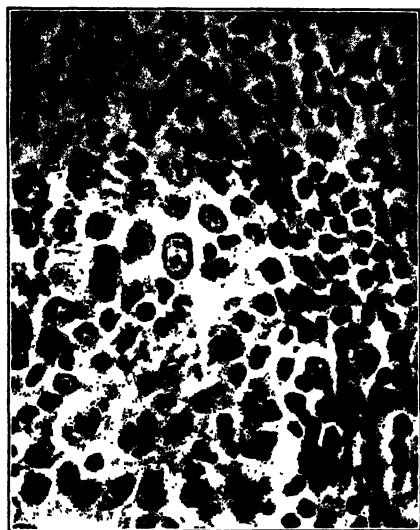


FIG. 145.—Lympho-epithelioma showing intermingling of epithelial and lymphoid cells.  $\times 340$ .

brane of the bowel to the irregular glands of the tumor is very sudden. The neoplastic glands are highly atypical with branching processes and darkly-staining cells which contrast strongly with the pale mucinous cells of the normal glands. (Fig. 146.) The lining cells are several layers in depth, and are not limited by the basement membrane, but invade the surrounding tissue. Mitoses are numerous. Most characteristic of all, new glands are found in abnormal positions, *e. g.*, deep to the muscularis mucosæ. Sometimes, particularly in the stomach, the glandular formation is lost, and the tumor assumes a scirrhous form with abundant stroma.

*Mucoid carcinoma*, formerly called colloid carcinoma, occurs principally in the large bowel, stomach, breast and bronchi. Two different

forms may be distinguished: (1) primary muroid carcinoma arising as a tumor of mucus-secreting cells; (2) a secondary form which is merely a muroid degeneration of a preëxisting adenocarcinoma. Only 15 per cent of cases belong to the true primary form, which is characterized by bulky gelatinous masses, loss of glandular arrangement (also seen in the metastases), large signet-ring cells showing abundant evidence of proliferation, and a high mortality. Many of the cells are greatly distended with mucin (Fig. 147), and large numbers of them disappear completely. In the secondary form the glandular arrangement is preserved with mucus in the acini (Fig. 148), the picture is one of advanced degeneration with little evidence of proliferation, and the malignancy is roughly proportional to the degree of mucus formation.



FIG. 148.—Adenocarcinoma, showing the sudden change from normal mucosa to the dark, irregular, infiltrating gland spaces on the right.  $\times 10$ .

**Carcinoma Simplex.**—Although this term is not commonly used, it is convenient for the purpose of classification. As a rule, it grows from the cubical epithelium of solid glands. The common site is the breast, just as the common site of squamous-cell carcinoma is the skin and the cervix, and the common site of adenocarcinoma is the stomach. Spread is principally by the lymphatics, but also by the blood stream. The cells are spheroidal or polyhedral, and are arranged in solid masses or columns. In *scirrhous carcinoma* the stroma is dense, the cell groups are small and often present a single column of cells, and the cells are compressed and stain darkly. (Fig. 149.) Mitotic figures are not numerous, for the tumor is not of rapid growth.

The dense stroma makes the tumor very hard. Most cancers of the breast are of the scirrhus type.

In the *medullary* or *encephaloid* form of carcinoma simplex the proportion of cells to stroma is reversed. (Fig. 150.) The cells are collected in large masses, are actively growing, and show many mitotic



FIG. 147.—Mucoid carcinoma. The tumor cells are greatly distended with mucin.  $\times 150$ .



FIG. 148.—Secondary form of mucoid carcinoma.  $\times 200$ .

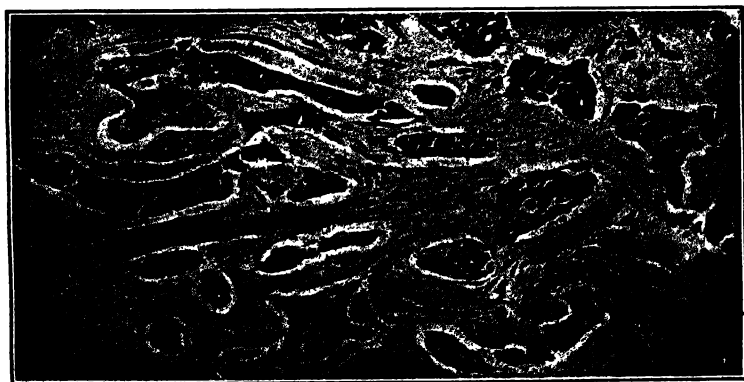


FIG. 149.—Scirrhus carcinoma of the breast. The compressed groups of tumor cells are separated by a dense stroma.  $\times 175$ .



figures. The stroma is scanty, so that the tumor is soft (encephaloid). Degeneration and necrosis are common. As one part of a tumor may show a scirrhus picture under the microscope and another a medullary picture, and as the primary tumor may be scirrhus while the metastases may be medullary, it is evident that the distinction between the two forms is in no way fundamental.

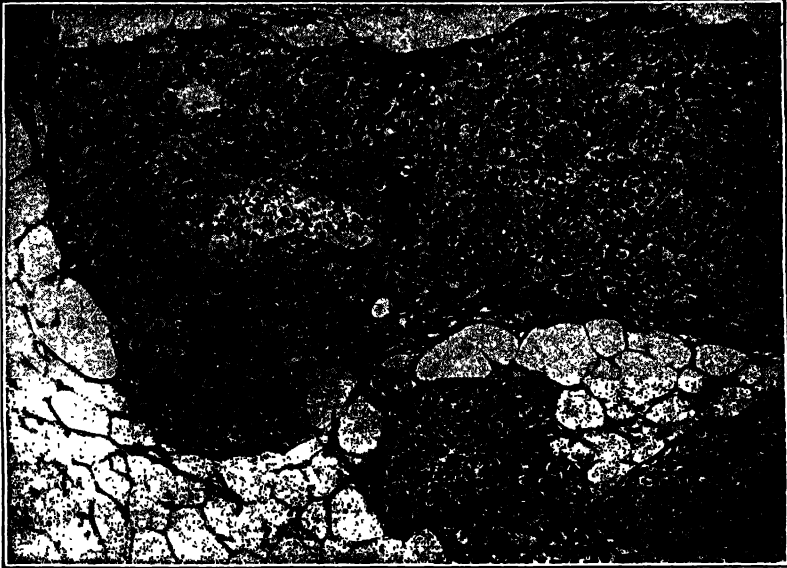


FIG. 150.—Medullary carcinoma of breast, highly cellular.  $\times 110$ .

**Adamantinoma.**—This is a rare epithelial tumor of the jaw which is one variety of *odontoma*. There are various views as to its origin, but it seems probable that it arises from the group of embryonal cells which comprise the outer epithelial layer of the enamel organ (Zegarelli), so that it may be called an *enameloblastoma*. It is composed of masses of epithelial cells which may become hollowed so as to give a glandular or cystic appearance. There is no constant microscopic picture. The cell type is the basal cell, but there may be all degrees of differentiation of the enamel organ. When differentiation is marked there may be an outer palisade layer of columnar cells, the enameloblasts, and a central core of "star cells" with large vacuoles and connecting cytoplasmic bridges. (Fig. 151.) Or there may be strands of epithelium of epidermoid type which branch and form a fantastic network. The undifferentiated forms consist entirely of basal cells. The tumor grows slowly and causes expansion of the jaw until a mere shell of bone is left. Cyst formation may occur. The tumor is usually innocent, but there may be invasion and, in rare cases, metastases.

Similar tumors are found in the stalk of the pituitary, where they are known as suprasellar tumors, and in the tibia. The pituitary stalk arises as an invagination of the oral epithelium, and as the enamel organ has a similar origin it is easy to understand why epithelial cells which retain their embryonic character should give rise to similar tumors in two different sites. The very rare tumors of the tibia are more of a puzzle, but may possibly be explained on a basis of abnormal embryonic epithelial invaginations.

Other varieties of odontoma are the composite odontoma and the dentigerous cyst. The *composite odontoma* is formed of various structures containing enamel and cement, and probably represents the fused masses of imperfectly formed teeth. A tooth is missing at the site of the tumor. A *dentigerous cyst* is a cystic odontoma formed from a tooth follicle. It may contain one or more imperfectly formed teeth. It is lined by epithelium. The slow growth of the cyst may cause marked enlargement of the jaw.



FIG. 151.—Adamantinoma showing palisade of enameloblasts and vacuolated cells.  $\times 220$ .

### TERATOMA

A teratoma is a composite mass derived from more than one germinal layer. In some there are representatives of all three layers. It is not a tumor in the strict sense of the word, but rather an attempted formation of a new individual within the tissues of the patient. A malignant growth may develop in a teratoma and may be carcinomatous or sarcomatous in type.

Every grade of complexity may be met with in a teratoma. At one end of the series is the parasitic fetus, an acardiac monster attached to a normal child. Or a jumbled mass of structures may be attached externally either to the upper jaw (*epignathus*) or in the sacral region (*sacral teratoma*). Or again such a mass may develop within the body, usually in the genital glands. The structure may be simpler, comprising only one or two tissues as in the embryoma (teratoma) of the kidney. Finally there may be inclusions of the surface (inclusion dermoids), which may cause tumor-like swellings.

In the early stage of the developing and segmenting ovum the first blastomeres are totipotent; they have the capacity of forming a new individual as shown by the occasional development of identical twins from the one ovum. The later blastomeres are multipotent, *i. e.*, they can form all of the three germinal layers. In the segmenting ovum primitive sex cells (germinal cells) are separated from the somatic cells and migrate finally to the testicle and ovary, where they develop into spermatozoa or ova. Theoretically it is quite possible for one of the primitive germ cells to be segregated either in the sex glands or in some other part of the body, where, if it could be stimulated to divide, it may form a teratoma which is an abortive attempt at the production of a new individual even to the extent of forming chorionic membranes, for the chorionic epithelium is merely a modification of the fetal ectoderm. A blastomere may also be segregated, and if it is stimulated to grow it will form structures derived from the three germinal layers, a confused jumble of tissues, but not including fetal membranes. MacCallum suggests that the teratomas may be divided into two main classes, the first representing the development of a primitive *germinal* cell, the second being derived from a segregated *somatic* blastomere. These two forms belong to different generations, the first being analogous to a true offspring, the second to a twin brother.

Jacques Loeb, as is well known, succeeded in inducing parthenogenesis in the unfertilized ova of sea-urchins and even frogs by employing various physical and chemical stimuli. The resulting animals were apparently normal except that they possessed no sex cells. In 1926 Bosaeus published an account of some extraordinarily interesting experiments on the parthenogenetic formation of teratomata. He removed an ovum from a frog's ovary, pricked it with a needle, and reimplanted the stimulated ovum into the body of the same frog. As the result of parthenogenesis a teratoma developed which was similar in type to some of the teratomas occurring in man. When the ovum was placed in the body of another frog it failed to develop.

A new possibility is provided by advances in experimental embryology. It is now known that differentiation depends on two factors: (1) chemical organizers, (2) susceptibility or "competence" of the cells to the action of the organizers. Both of these change as development proceeds. Thus there are primary, secondary and tertiary organizers, and the susceptibility of the cells alters with the course of development. When there is perfect balance between organizers and susceptibility, differentiation proceeds normally, but if organizers are produced too abundantly or too early or if susceptibility persists beyond the period at which it is normally lost, the result may be uncontrolled differentiation with the production of a jumble of structures so characteristic of teratomas.

Perhaps the most varied structures are encountered in teratomas of the genital glands. In the dermoid cyst of the ovary are found skin, hair, sebaceous material, teeth, bone, brain, thyroid, etc. In

teratoma of the testicle glands, cartilage, muscle, brain, and even choroid plexus may occur (Fig. 152).

**Inclusion Dermoids.**—Although these have the same name as the congenital tumors occurring in the genital glands, their origin is quite different. They may be divided into congenital and implantation dermoids; in both cases there is inclusion of dermal and epidermal structures.

**Congenital Dermoids.**—Congenital dermoids are inclusions of dermal tissue along the line of the embryonic fissures. Dermal tissue, it may

be with hair and cyst formation, is found in the middle line of the abdomen and chest (mediastinal dermoid), in the skull (line of attachment of dura mater to tentorium cerebelli), in the line of the thyroglossal duct and the duct leading from pharynx to pituitary, and at the site of the branchial clefts, particularly the second.

**Implantation Dermoids.**—Implantation dermoids are the result of a small piece of skin being implanted in the deeper tissues, usually as the result of trauma with a pointed instrument. A small cyst lined by epidermis is formed. These cysts are most common on the hands of manual laborers.



FIG. 152.—Choroid plexus in teratoma (chorione epithelioma) of testicle.  $\times 175$ .

be with hair and cyst formation, is found in the middle line of the abdomen and chest (mediastinal dermoid), in the skull (line of attachment of dura mater to tentorium cerebelli), in the line of the thyroglossal duct and the duct leading from pharynx to pituitary, and at the site of the branchial clefts, particularly the second.

individual specimens. Two pitfalls may be mentioned at this point; these are carcinoma *in situ* and benign epithelial invasion.

**Carcinoma in situ** is a term suggested by Broders for a condition in which the epithelium shows definite evidence of malignancy such as irregularity in size and shape of the cells, hyperchromatism, etc., but definite invasion of the surrounding tissue has not occurred. (Fig. 153.)

**Benign epithelial invasion** is the converse condition. Here the epithelium retains its normal character, but has penetrated deeply into the underlying tissue. The best example is seen in the gall-bladder, where newly-formed glands may penetrate as far as the serous coat (chole-

## THE PATHOLOGICAL DIAGNOSIS OF CANCER

The recognition, especially the microscopic recognition, of malignancy may be very easy, but it may be exceedingly difficult, and the best pathologists will be found to differ in their diagnosis of indi-

cystitis glandularis proliferans) without the condition becoming malignant. (Fig. 154.) Other examples are seen at the edge of a chronic ulcer of the skin or the stomach, and in the uterus, ureter and other organs lined by epithelium.



FIG. 153.—Carcinoma *in situ*.  $\times 125$ .



FIG. 154.—Benign epithelial invasion in gallbladder. New glands have penetrated to serosa.  $\times 12$ .

**Autopsy Examination.**—The postmortem examination of most cases of tumor formation is simple enough, for the nature of the primary growth and metastases can usually be inferred from the location of the tumor and its gross characteristics followed later by microscopic examination. But there may be difficulties. It may be hard to know which is the primary and which the secondary growth. For instance, tumors may be found in the brain, lung, and adrenal, and these are composed of undifferentiated round cells. Our knowledge of the general behavior of tumors tells us that if the patient is a child under the age of four years the primary tumor is almost certainly neuroblastoma of the adrenal medulla; on the other hand, if the patient is an adult the primary growth is equally certainly an anaplastic carcinoma of the lung. In neither case could the primary growth be in the brain, because the glioma though malignant does not metastasize. The same pathological reasoning can, of course, be applied to the living patient. In some organs a primary malignant tumor is very rare, *e. g.*, liver, spleen, heart. When a tumor is found in one of these

organs it is most likely secondary and a careful search must be made for a primary tumor elsewhere. It is easy to overlook carcinoma in the lowest part of the rectum and in the prostate.

**Biopsy Examination.**—A biopsy is the examination of a piece of tissue removed during life. The fate of the patient may depend on a correct report, and it is the duty of the surgeon to take certain precautions in removing the specimen. In the case of a doubtful breast tumor the entire lump must be removed, not a small piece of it. Whether the tumor is innocent or malignant the lump must come out, and if only a portion is removed the essential lesion may be missed. Similarly a small ulcer of the lip should be excised entire and then examined. The surgeon will not wish to remove a large ulcerated area on the tongue, cervix or rectum if it should prove to be innocent. Here it is sufficient to excise a piece of the edge of the ulcer. If the lesion on the tongue or cervix is malignant it is an epithelioma which is recognized by infiltration of the deeper parts. The section must therefore go deep. A shaving of the surface is worse than useless. In the rectum a malignant tumor will be an adenocarcinoma, so that a more superficial section will suffice. The tissue must be placed at once in a fixative (10 per cent formalin, etc.). This is of particular importance when the specimen has to be sent in from a distance. The worst thing that can happen to a small piece of tissue is to be allowed to dry.

Tumors of lymph nodes and bone are particularly hard to diagnose by physical examination, so that the clinician turns to the pathologist for assistance. Removal of an isolated lymph node is a harmless procedure, and sometimes gives valuable information. But removal of a lymph node in diseases of the lymphatic system is much overdone. If the physician, after a careful clinical and blood examination, is still in doubt, the pathologist is also likely to be in difficulty. As regards microscopic diagnosis in general, one of the most difficult tasks is to differentiate between sarcoma and inflammatory tissue.

The dangers of the biopsy are often discussed. Theoretically it might well be a means of spreading a malignant tumor owing to the opening up of bloodvessels and lymphatics. In actual practice this danger appears to be negligible. In the largest surgical clinics where biopsies are done all the time the percentage of metastases is certainly no higher than when this method is not used. F. C. Wood performed biopsies without any special precautions on a large number of rats with carcinoma, and an equal number were left untouched. At the end of some months the animals were killed, and no difference in number of lung metastases was found in the two sets of animals. No one is afraid of using the diagnostic curettage, where there ought to be every chance of spreading the malignant cells. The biopsy should be used more, not less.

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## CHAPTER XI

### VITAMIN DEFICIENCY

AN adequate supply of protein, carbohydrate, fat, and mineral salts is not sufficient for the needs of the living body. F. G. Hopkins, McCollum, Funk, and others have shown that certain accessory food factors are also necessary for life. They are therefore called vitamins. Some of them exercise a remarkable regulating effect over such fundamental processes as calcification and bone formation. Moreover, in the absence of vitamins neither proteins, carbohydrates, fats, nor salts are properly utilized. The vitamins are therefore true regulators. They are synthesized by plants, not by animals. Man's supply therefore comes either directly from plants or from animals which have eaten plants and stored up the vitamins.

For long we knew no more of the nature of the vitamins than of the nature of electricity, although both could readily be recognized by the effects which they produced. Now many of them have not only been obtained in chemically pure form from their sources in nature, but have been synthesized in the laboratory. They need only be present in minute amounts, but their absence (avitaminosis) leads to profound pathological changes. Some of these deficiency diseases such as rickets and scurvy have been known for centuries and empirical methods of treatment have been successfully employed. The old explorers recognized the value of fresh fruit in the prevention of scurvy, and cod-liver oil has been used for the treatment of rickets for more than a hundred years.

Avitaminosis or insufficiency of vitamins may be a manifestation of *primary* malnutrition caused by dietary inadequacy; even the so-called bland diet of a hospital régime may lead to vitamin deficiency. Much malnutrition, however, is *secondary* to disease. There may be interference with absorption from the bowel due to intestinal lesions. Diffuse disease of the liver such as cirrhosis may diminish the storage capacity of the liver. Fever, hyperthyroidism and pregnancy may accelerate metabolism and thus increase the nutritional requirements of the body. Even glucose solution given over a period of several days will wash out the reservoirs of thiamine, and may lead to the development of acute symptoms such as severe vomiting and paralytic ileus.

Owing to former ignorance as to the composition and nature of the vitamins it has not been possible to give them satisfactory names. They are usually called after the names of the alphabet. They may be called after the diseases which their absence will induce. Finally they are divided into the two groups of fat-soluble and water-soluble vitamins. The fat-soluble vitamins are A, D, E, and K; they are found principally in fats and oils. The water-soluble vitamins are B and C.

The order here adopted is irregular, but it has helped the writer and it may possibly be of assistance to the reader. The six vitamins are divided into three groups as follows: (1) A and D; (2) the B complex; and C; and (3) E. The first group includes the chief of the fat-soluble vitamins. Vitamin A should be associated with vitamin D in the reader's mind, because they are both contained in cod-liver oil, and at first were not recognized separately, being grouped together as vitamin A; it was only later that vitamin D was separated from the group. The second group includes the water-soluble B complex or thiamine and C. B prevents beri-beri and C prevents scurvy, the alliteration lightening the task for the memory. As beri-beri is a form of neuritis, B, or thiamine may be regarded as an antineuritic vitamin. In pellagra, the disease associated with the absence of vitamin nicotinic acid, another part of the B complex, the nervous system is again involved. The water-soluble forms are stored in much smaller amounts than the fat-soluble, and the reserves of vitamin B<sub>1</sub> are rather quickly exhausted. The third group comprises vitamin E, of less importance in medicine, a fat-soluble vitamin; when absent from the food sterility may result.

As Wolbach points out in his excellent review of the subject, some of the lesions accompanying vitamin deficiency are primary and specific, while others are secondary and non-specific. The primary lesions are all manifestations of retardation or suppression of normal processes. The lesions may be biochemical and invisible, rather than histological and visible. These biochemical lesions may be the result of interference with intracellular respiration, for several vitamins appear to regulate the action of the enzymes essential for intracellular oxidations and reductions, if indeed they are not related to these enzymes chemically.

Although intensive investigation has been carried on with regard to individual vitamins, it must be remembered that malnutrition is often not the result of absence of any one vitamin, that the administration of a single vitamin in a chemically pure state may not serve to correct the condition, and that no laboratory mixture is the equal of a good well-balanced diet. Moreover it is not possible to keep an animal alive on a vitamin-free diet to which has been added all the pure vitamins known.

**Vitamin A.**—Vitamin A is found in bright yellow foods such as butter, eggs, corn, sweet potatoes. Being fat-soluble, it is stored in the fat of animals, and it is present in greatest abundance in cod-liver oil (although much is lost in the process of refining), but fresh milk contains an adequate supply for the growing child, especially when combined with yolk of eggs. Moore has shown that animals can synthesize it in the liver from the vegetable pigment carotene, so that it may be given directly as cod-liver oil or indirectly as vegetables. The conversion takes place in the liver through the action of an enzyme. The vitamin has been isolated in chemically pure form, and has been synthesized.

Vitamin A gives a green fluorescence in ultra-violet light, which disappears rapidly. Popper points out that similar fluorescence, presumably due to vitamin A, can be seen in frozen sections of certain tissues. It is most marked in the liver, adrenal cortex, and corpus luteum. In hypervitaminosis A the amount is increased.

The basic lesion of vitamin A deficiency is atrophy of columnar epithelium and a substitution of stratified keratinizing epithelium due to proliferation of the basal cells, i. e., a keratinizing metaplasia, which may be regarded as an attempt at repair following atrophy (Wolbach). In the human infant this occurs in the conjunctiva, nasal mucosa, accessory nasal sinuses, salivary glands, trachea, bronchi, pancreas, renal pelvis, ureters, and uterus. The commonest and earliest change is in the trachea and bronchi, and death is often due to pneumonia. The lumen of the ducts is blocked by desquamated keratinized cells so that cysts are formed in glands, bronchiectatic cavities in the lungs, etc. In the eye a late effect is xerophthalmia. The cornea dries up (xeros, dry) and becomes ulcerated and infected. This is due to involvement of the lacrimal glands, as a result of which the tears are no longer produced and the cornea is not bathed with fluid as it should be. Mellanby suggests that the corneal lesion may be due to loss of the neurotrophic control of the cornea by the ophthalmic division of the trigeminal nerve, for degeneration of the myelin sheath of that nerve develops at the same time as the corneal degeneration, and in early cases both lesions are recovered from as the result of adding vitamin A to the diet. The salivary glands also become dried up. Xerophthalmia is rarely seen in Europe and America, but in Japan and other eastern countries poorly-nourished children not infrequently develop the condition.

It has been suggested by E. Mellanby that vitamin A protects the body against infection, and it has been called the anti-infection vitamin. Possibly the epithelial metaplasia which follows deficiency of the vitamin is responsible for a local lowering of resistance to infection. It is certainly the case that animals on a diet deficient in vitamin A are peculiarly liable to develop local infections. Therapeutic possibilities suggest themselves, but it is not wise to say more than this.

Animals on a diet deficient in vitamin A may develop degenerative lesions in the posterior and lateral columns of the spinal cord. These are very similar to the lesions (combined degeneration) often seen in the cord in severe cases of pernicious anemia. It is possible that there are two dietetic factors in the production of the advanced picture of pernicious anemia: (1) a water-soluble factor concerned with the formation of the red blood cells, and (2) a fat-soluble factor absence of which leads to degeneration in the central nervous system.

Testicular degeneration affecting the seminiferous epithelium develops in rats on a deficient diet. This is similar to the change caused by vitamin E deficiency.

Night-blindness (hemeralopia, more correctly nyctalopia) has long been known to be benefited by cod-liver oil. Hippocrates recommended

ox liver dipped in honey for a cure, and in Newfoundland cod's liver is a popular remedy. Any source of vitamin A will effect a cure. Night-blindness is due to exhaustion of the visual purple after prolonged exposure to brilliant sunlight, and lack of vitamin A interferes with regeneration of the visual purple.

**Vitamin D.**—Much of the romance of the vitamins centers around this member of the group. Being fat-soluble it was at first confused with vitamin A, which is also fat-soluble. Later it was found that the antirachitic factor in cod-liver oil was quite different from the antixerophthalmic factor. Milk, butter, egg-yolk, and other fats contain vitamin D, but far the most abundant supply is cod-liver oil. The vitamin has been obtained chemically pure. It has the same chemical formula as ergosterol,  $C_{27}H_{41}OH$ , and appears to be an isomer of that substance, being formed from it as the result of the action of ultra-violet light.

Vitamin D *controls calcium metabolism*. Whether or not it acts in conjunction with the parathyroids is uncertain; probably not. The vitamin has two fundamental and independent actions: (1) to increase the absorption of calcium from the gastro-intestinal canal, and (2) to increase the excretion of phosphorus in the urine. When the vitamin is deficient or absent from the diet there is great interference with calcification and *rickets* results. What is actually interfered with is the calcification of the proliferating cartilage at the epiphyses. This must be distinguished from true ossification which consists in the replacement of the calcified cartilage by true bone and bone-marrow. The complex subject of rickets and the several etiological factors involved will be discussed in connection with the diseases of bones, and will therefore not be considered here.

The work of May Mellanby has shown what an important influence vitamin D has on the *development of the teeth* both in the experimental animal and in the child. When the diet contains an abundance of vitamin D (milk, egg-yolk, etc.), the teeth are even, bright, shiny, and well formed. With a diet poor in vitamin D, especially if it is rich in cereals, the teeth are uneven, poorly calcified, dull, and discolored. *Caries* is a disease of poorly developed and poorly calcified teeth, but there is no general agreement as to the relationship between avitaminosis and the development of human caries. The matter is discussed further in Chapter XXXV. Even when caries has started in poorly-formed teeth it can be arrested by putting the child on an adequate diet owing to the formation of secondary dentine as the result of the action of vitamin D. Cereals have a remarkable effect both in interfering with calcification and in encouraging caries. The inhabitants of the little island of Tristan da Cunha in the south Atlantic have the most perfect teeth of any Anglo-Saxon community in the world, entirely free from caries although there is not a toothbrush on the island. Cereals are unknown there, for the enormous number of rodents has made their cultivation impossible.

The possibility of *hypervitaminosis* deserves mention, although

there is no danger of this with ordinary therapeutic doses. When large over-doses of vitamin D (irradiated ergosterol) are given there is hypercalcemia and hyperphosphatemia. If the diet is deficient in calcium there is removal of calcium from the bones. If, on the other hand, the diet is rich in calcium the bones are much less affected, but there are calcareous deposits in many of the tissues, being most marked in the renal tubules and the walls of the arteries. Renal insufficiency favors calcification of the soft tissues, for it interferes with the excretion of phosphorus, and high serum phosphorus is even more important than high serum calcium in promoting calcification of soft parts.

**Vitamin B.**—Vitamin B, one of the water-soluble vitamins, is a complex substance containing a number of components; for that reason the term vitamin B complex has come into use. The complex may be defined as the collection of vitamins present in the yeast cell. New factors are continually being separated but at the present time the most important are thiamin or B<sub>1</sub>, riboflavin or B<sub>2</sub> (formerly known as vitamin G), pyridoxine or B<sub>6</sub>, nicotinic acid, and pantothenic acid. To these may be added paraminobenzoic acid, inositol, biotin and choline. The chemical formula of each member of the B group is now known, and each has been synthesized in the laboratory. The vitamin is one of the most widely distributed, being present in all natural foodstuffs, but much of it is lost in the process of refining and of converting natural foods into artificial foods, as in the case of white bread, polished rice, etc.

*Thiamin* or B<sub>1</sub> is the antineuritic vitamin. It is the heat-labile component of the complex, and is an essential factor in enzyme systems concerned with carbohydrate metabolism. When rice is polished the skin and the embryo are removed, and it is these which contain the vitamin. Birds fed on polished rice develop an avitaminosis known as the polyneuritis of birds or rice disease. This is characterized by extreme ataxia followed by paresis due to peripheral neuritis, together with anemia, lymphopenia, and hyperglycemia. In experimental observations on pigs, Follis and his associates found focal and diffuse myocardial necrosis associated with marked cardiac dilatation in animals dying of thiamin deficiency. Thiamin deficiency is involved in the neuritis recurring in chronic alcoholism, pregnancy and diabetes. Its most striking manifestation is beri-beri, although this is certainly not an example of pure vitamin B<sub>1</sub> deficiency. Milder forms of thiamin deficiency, which may be due to the use of a diet composed largely of white bread, are not uncommon. They are characterized by symptoms suggesting myocardial disease, such as tachycardia, dyspnea, edema, and enlargement of the heart. These may be associated with numbness and tingling of the hands and feet.

*Riboflavin* or B<sub>2</sub> plays an important part in normal tissue respiration. Mild forms of ariboflavinosis are not uncommon among the under-nourished and those who subsist on absurdly inadequate diets with the object of improving their figure. Severe eye manifestations are seen principally in the southern states of America. There may be cheilosis

(fissured lesions at the corners of the mouth), erosions around the eyes, and rough desquamation of the sides of the nose. The most serious disturbances are those involving the eye. In those whose occupation exposes them to bright light (including workers with the microscope) there may be photophobia, eye fatigue, redness of the conjunctiva and lower lids. The earliest and most common sign is circumcorneal injection, best revealed by the slit lamp. In more advanced cases there is invasion of the cornea by capillaries arising from the limbic plexus with final corneal opacity and keratitis.

*Nicotinic acid* is necessary for normal tissue oxidation. It is known as the P—P or pellagra-preventing factor, and is of great value in treating the major symptoms of pellagra, although that disease is not an example of a pure avitaminosis but is apparently due to multiple nutritional deficiencies. *Pellagra* is a disease of maize-eating countries (Italy, the southern United States, etc.), but is not confined to these regions. There is a curiously symmetrical pigmentation and erythema followed by desquamation of the exposed parts of the body (face and back of hands), gastro-intestinal disturbance, and finally nervous and mental disorders. Muscular weakness is marked. The chief microscopic lesions of the skin are a severe grade of hyperkeratosis in the epidermis and edema and congestion in the dermis, with some round-cell infiltration in the superficial layers of the dermis.

Gillman and Gillman, by means of repeated liver puncture on South African negroes suffering from pellagra, have shown that fundamentally important changes take place in the liver in the course of the disease. The first change is extensive fatty degeneration. This is followed by a massive accumulation of iron pigment in the liver cells, necrosis of these cells, and finally cirrhosis. This of course is the picture of hemochromatosis. According to Gillman and Gillman 20 per cent of pellagrins in South Africa show evidence of incipient or frank cirrhosis of the liver.

*Pantothenic acid* is essential for the growth of many bacteria. Deficiency of this vitamin has been studied chiefly in rats and chicks. Two lesions of rats bear some resemblance to pathological conditions observed in man, namely acute necrosis of the liver and the bilateral necrosis of the renal cortex which is a rare complication of human pregnancy. Vitamin B-deficient diet is poor in choline, and it is possible that this lack is responsible for the lesions in the liver and kidney (György and Goldblatt).

**Beri-beri.**—Beri-beri is a disease of eastern countries due to eating polished rice. The principal features are peripheral neuritis, edema, and myocardial weakness, a triad of symptoms which is found in no other disease. The disease differs in some respects from the experimental rice disease of birds. In both there is polyneuritis, but the birds do not show the edema and cardiac failure, while the beri-beri patients do not show the anemia, lymphopenia, and hyperglycemia characteristic of the experimental disease. Vitamin deficiency is an essential factor in the production of beri-beri, but it is rarely so com-

plete as to be the sole agent, and it is probable that the addition of an infection is needed to give the classical picture.

Among the autopsy findings are edema of the legs, fluid in the serous sacs, and marked enlargement (both hypertrophy and dilatation) of the right side of the heart. In addition there is marked degeneration of the peripheral nerves (Wallerian degeneration) and degenerative changes in the motor nerve cells of the anterior horn of the spinal cord and of the sensory nerve cells in the posterior root ganglia.

A form of pellagra may occur as the result of chronic gastro-intestinal disease. The patients show the characteristic gauntlet or glove dermatitis, but the other signs are not so marked as in the edemic form. Among the conditions which have given rise to this form of deficiency disease are extensive cancer of the stomach, postoperative obstructive lesions of the small bowel, and inflammation and cancer of the colon.

**Vitamin C.**—The other water-soluble vitamin is the antiscorbutic one. Vitamin C is present in all fresh fruits and vegetables, being particularly abundant in tomato, orange, lemon, and grape-fruit. It is present in smaller amount in fresh meat and milk. Steffanson maintained himself in the Arctic on a diet of fresh meat alone without developing scurvy. The vitamin is easily destroyed by heat, so that boiled or pasteurized milk may be completely lacking in it. It is the duration of heating rather than the actual temperature which seems to matter. The drying of fruits also destroys the vitamin.

Vitamin C is identical with an hexuronic acid (ascorbic acid), isolated in crystalline form from adrenal cortex as well as fruit juices. It can be demonstrated in the gross by an intense blackening produced by silver nitrate on exposure to light. The adrenal cortex in scurvy is depleted of fat and cholesterol as well as of vitamin C. In scurvy the level of ascorbic acid is low in the urine and very low in the blood. In health the tissues should be saturated with the vitamin, and when the dye 2:6-dichlorophenolindophenol is injected intradermally it is discolored. This does not occur when the vitamin is deficient.

**Scurvy (Scorbutus).**—Scurvy is the result of a deficiency of vitamin C in the food. Once the scourge of sailors and explorers who were unable to carry supplies of fresh fruit and vegetables, it is now seldom seen in the adult since it was found that lime juice would act as an excellent preventive. The true reason for the prophylactic power of the lime juice is, of course, a modern discovery. In war, in beleaguered cities, etc., scurvy may still prove a menace. In some countries the potato is the chief antiscorbutic article of diet during the winter months. In such a country as Ireland a potato famine has often been accompanied by an outbreak of scurvy. But it is in children that the disease is most likely to be seen at the present day, for modern methods tend to destroy the vitamin in the child's natural food. Scurvy is practically never met with in breast-fed children. But it may develop in bottle-fed babies, for the sterilization of the milk (boiling or pasteurization) destroys the antiscorbutic vitamin. Even keeping the milk instead of using it fresh lessens the vitamin content.

The addition of orange juice to sterilized milk restores to the full its antiscorbutic power.

The obvious *lesions of scurvy* are hemorrhages and changes in the bones. But the essential underlying lesion is an inability of the supporting tissues to produce and maintain intercellular substances. The effect is on cells of mesenchymal origin in contrast to the ectodermal and entodermal effects of vitamin A deficiency. The intercellular substances concerned are the collagen of all fibrous tissues, the matrix of bone, dentine and cartilage, and all non-epithelial cement substance including that of vascular endothelium. The weakening of the capillary walls is responsible for the hemorrhage which forms so prominent a feature of the disease. There may be hemorrhages in the skin, mucous membranes, muscles, lungs, nerve sheaths, under the periosteum, and into the joints. Hemorrhage in the adrenals is one of the earliest changes in experimental scurvy. The gums are soft, spongy, and bleed readily and the teeth may fall out. If the teeth are bad, the mouth and breath become very foul. Bone formation is brought to a standstill, and as the normal process of bone absorption still goes on the bones become rarefied and fragile. The formation of the cartilaginous and bony matrix ceases, the osteoblasts become elongated, assume the shape of fibroblasts, proliferate, and accumulate between the bone and periosteum, forming a thick cellular layer devoid of matrix into which massive hemorrhages occur. Characteristic lesions are seen at the epiphyseal line. The normal narrow line of ossification is broadened and dense, giving a pathognomonic picture in the roentgen-ray film. Fragments of bone are scattered about, and hemorrhages are frequent. It is not a disturbance of calcification as in rickets, but of ossification. When a proper diet is given, osteogenesis is rapidly resumed.

*Infantile Scurvy (Barlow's Disease).*— Infantile scurvy is similar to adult scurvy, but the symptoms due to the bone lesions dominate the picture. The legs are so tender that the child screams if they are even touched. This tenderness is due to subperiosteal hemorrhages. Growth of the bones is naturally in abeyance. The gums may be tender and bleeding. The disease usually appears in the second half of the first year. After the second year it is seldom seen in an acute form as the diet is more varied, but there may be minor manifestations which are often unrecognized.

The *condition of the blood* is of interest in scurvy whether adult, infantile or experimental. In all forms a secondary anemia develops, and the red marrow shows a corresponding picture, *i. e.*, disappearance of fat and cellular hyperplasia. Treatment with orange juice or a diet rich in vitamin C produces a remarkable effect on the blood picture, for not only is there rapid regeneration of blood but there is an immediate increase in the number of reticulocytes. Treatment with liver extract from which vitamin C has been removed has no effect on the reticulocytes. Bone-marrow obtained by sternal puncture after orange-juice therapy shows a marked increase of nucleated red cells, some of which show mitoses.



It is important to recognize that in the case of vitamin C as with the other vitamins there may be enough of a deficiency to produce symptoms of ill-health without the typical full-blown picture of scurvy. Mild manifestations of vitamin C deficiency are not infrequently seen in what is known as "bachelor scurvy," a condition of anemia, weakness, and occasional ecchymoses which develops in elderly men who live alone and who cook their own meals.

**Vitamin E.**—This is the antisterility vitamin and belongs to the fat-soluble group. It is present in growing things, and is especially abundant in the wheat germ, but is contained in sufficient quantity in lettuce, meat, whole wheat and other foods. Deficiency of the vitamin produces different lesions in the two sexes. In the male the spermatozoa are destroyed, and there is finally degeneration of the entire seminiferous epithelium. In the female the ovaries do not appear to be injured, fertilization of the ovum occurs, and gestation commences, but about the eighth day in the rat pathological changes set in, in the placenta and the fetus dies and is absorbed. In addition to its effect on the reproductive function, vitamin E is a necessary factor for the preservation of the integrity of skeletal muscle. When female mice are maintained on a vitamin E low diet but are given a single dose of vitamin to ensure the birth of living young, the offspring show marked necrosis of skeletal muscle in 20 per cent of cases with early calcification (Pappenheimer).

**Vitamin K.**—In 1930 Dam, of Copenhagen, noticed that chicks fed on a deficient diet developed hemorrhages owing to the loss of coagulating power of the blood, and that this was prevented by giving alfalfa. The coagulation factor in the alfalfa was extracted, crystallized and finally synthesized. It was called Koagulationsvitamin or vitamin K. The vitamin is necessary for the manufacture of prothrombin, so that when the vitamin is deficient the prothrombin in the blood is low. Estimation of the plasma prothrombin thus affords a simple method of determining if there is deficiency of vitamin K. Such deficiency in man is probably never due to lack of the vitamin in the food. It does occur in obstructive jaundice and in hemorrhagic disease of the newborn. Unless bile is present in the bowel vitamin K is not absorbed, prothrombin is not formed in sufficient amount, and hemorrhage occurs. In *obstructive jaundice* bile is prevented from entering the bowel. This explains the marked tendency to bleeding after operations on jaundiced patients. The bleeding can be prevented by the administration of bile and vitamin K, or by giving the synthetic vitamin by mouth (the synthetic product is absorbed without the assistance of bile), or intravenously. If the liver is severely damaged (cirrhosis, amyloid, etc.) the administration of vitamin K is of no avail, because it is in the liver that the prothrombin is produced which is essential to coagulation. The explanation of *bleeding in the new-born* is that vitamin K is produced by the action of intestinal bacteria, and these are absent during the first few days of life. At birth the baby has sufficient prothrombin from the maternal blood, but this rapidly

falls, and there may be severe and even fatal hemorrhage, particularly intracranial. This can be prevented by giving the mother vitamin K before delivery.

Most of the work on the vitamins has consisted of devising special food mixtures and inducing in experimental animals such striking pictures as those of scurvy, rickets, and beri-beri. It is probable that in man, particularly in children, many minor disturbances may be due to deficiencies in diet. The reader is referred to McCarrison's very interesting book for a discussion of this matter. McCarrison is of the opinion that much of the gastro-intestinal disorder so common at the present day is to be attributed to a deficient and ill-balanced diet. He says that the health of the alimentary canal is dependent on vitamins B and C, that lack of B gives rise to changes like colitis, while lack of C causes congestion and hemorrhages of the bowel even though the patient never develops the classical manifestations of scurvy. He shows that many of the organs atrophy in deficiency disease, but that in all of the deficiencies there is a remarkable enlargement of the adrenals.

It is possible that some forms of colitis may have a deficiency basis. Cases of *celiac disease* (meaning disease of the abdomen) may clear up rapidly when the diet contains the proper vitamins. It is a peculiar condition affecting bottle-fed babies, coming on between the ages of nine months and two years, and characterized by cessation of growth, diarrhea, large whitish frothy stools, abdominal distention, weakness, and a frequent association of scorbutic symptoms. Vitamin A deficiency may play a part.

The laboratory worker concentrates on producing a single deficiency in the experimental animal. In man many of the deficiency diseases are multiple deficiencies, for dietary deficiency is rarely confined to a single factor, at least in this country. For this reason the administration of pure vitamins is rarely sufficient for a cure, and is never a substitute for a good general diet. In 1939 over \$86,000,000 were spent by the United States public in buying vitamins. It is better and infinitely cheaper to get one's vitamins from the grocery store, where they have been manufactured by Nature, than from the drug store where they have been manufactured by man.

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## CHAPTER XII

### INJURIES CAUSED BY PHYSICAL IRRITANTS

#### HEAT

**Burns.**—The effects of a burn depend on two quite different factors: (1) its severity, and (2) its extent. An extensive burn of moderate severity may be as serious as a severe but localized burn. There are three degrees of severity. The *first degree* indicates damage to the epidermis with hyperemia and vesication, the *second degree* involves dermis as well as epidermis with varying amounts of damage to sebaceous and sweat glands and their hair follicles, whilst in the *third degree* the entire thickness of the skin is destroyed.

The *systemic effects* of severe burns are very important, and there is much difference of opinion as to their explanation. When the burn covers a large surface the patient may die within twenty-four hours of shock—at least the symptoms are the same as those of traumatic shock. If death does not take place within that period a series of apparently *toxic symptoms* develop, such as delirium, vomiting, bloody diarrhea and circulatory failure. In experimental burns immediate removal of the burned area prevents the onset of these symptoms, and if the burned area is transplanted into a normal animal the symptoms will appear in that animal. Such facts suggest that some at least of the symptoms are due to the absorption of toxins from the burnt surface, but there is no agreement as to the nature of the toxin. Histamine may be liberated and may be responsible for the shock. A deep but limited burn may be shut off from the general circulation by local thrombosis, so that general toxic symptoms fail to develop.

Another factor which may be of even greater importance is concentration of the blood, which rapidly occurs in superficial burns owing to a great outpouring of fluid through the damaged capillaries into the subcutaneous tissue. (Fig. 155.) This sudden local edema may lead to a remarkable concentration of the blood as shown by hemoglobin estimation (Underhill), and this leads in turn to circulatory failure and oxygen starvation of the tissues. The hemoconcentration sends up the red cell count, sometimes as high as 8,000,000. These features are, of course, those of shock. It is probable that the hemoconcentration is due to general as well as local loss of fluid. Such loss is the essence of the shock syndrome, and may be attributed to toxic action on capillary endothelium throughout the body increasing its permeability. Ham has shown by experiments on the skin of the young hog that when only the superficial layer of dermis is involved tanning of the skin by means of tannic acid prevents fluid loss from the

superficial plexus of vessels which are normally concerned in temperature regulation. In deeper burns there is no such effect, because the fluid loss is from vessels which cannot be reached by the tanning process.

Autopsy on the early cases shows little beyond congestion of the brain and meninges. At a slightly later stage the autopsy picture of shock may be presented, *i. e.*, congestion, edema and hemorrhage in the viscera, especially the lungs, and fluid in the serous cavities. After about the third day lesions may appear which for want of a better word



FIG. 155

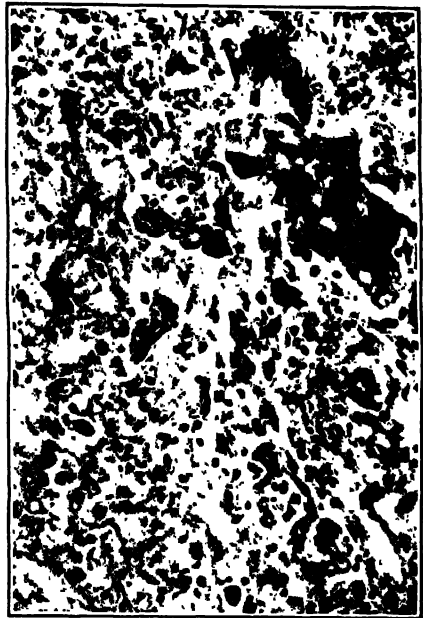


FIG. 156

FIG. 155.—Severe burn of skin showing great edema and thrombosed vessel.  $\times 175$ .  
 FIG. 156.—Necrosis of liver in a case of burns treated with tannic acid.  $\times 120$ .

may be called toxic. Cloudy swelling is marked in the liver, kidney, etc. Necrosis of the liver is often found in fatal cases by the third or fourth day, most marked in the central and mid-zone areas. This necrosis may be extremely severe, so that the picture may actually resemble that of yellow atrophy of the liver. (Fig. 156.) Mitoses are common and intranuclear inclusions like those of yellow fever may be present (Belt). These lesions have become noteworthy since tannic acid became the accepted treatment of burns. Wells and his associates have produced identical and fatal lesions by the subcutaneous injec-

tion of tannic acid. It seems probable that the hepatic necrosis is due to the tannic acid treatment, which for long has been a favorite method of dealing with burns. It is not a characteristic lesion of fatal cases not treated with tannic acid (Baker). The matter is complicated by the fact that tannic acid tides the patient with burns over the first few critical days, and it is only after this interval that the liver lesions either of burns or tannic acid become apparent. In the Hospital for Sick Children, Toronto, careful autopsy examination on tanned and untanned cases of burns showed liver necrosis in 61 per cent of the tanned cases, whereas no liver necrosis occurred in the untanned group (Erb, Morgan and Farmer). I have seen bilateral necrosis of the renal cortex due to thrombosis. A large amount of blood pigment may be deposited in the kidney, particularly in the straight tubules. The adrenals are much swollen, deep red in color, and show numerous hemorrhages. Hemorrhages are present under the endocardium and epicardium. Acute duodenal ulcers occasionally develop, perhaps due to the action of toxins absorbed, perhaps to emboli.

**Heat Stroke.**—This is essentially a paralysis of the heat-regulating mechanism caused by exposure to excessive heat. The actual temperature required depends on the humidity and varies with different persons. Heat loss is largely regulated by sweating, and some people can perspire very little. Complete saturation of the air with water vapor when the temperature is 90° F. causes an uncontrollable rise of body temperature. When the air temperature exceeds the body temperature all loss of heat by radiation ceases, and regulation of temperature is entirely dependent on sweating. A distinction is often drawn between heat exhaustion and heat stroke. It is doubtful if they differ other than in degree. In *heat exhaustion* the heat-regulating mechanism is severely strained, and the patient manifests weakness, pallor, stupor, and low blood-pressure. The temperature may be slightly raised, but on the other hand it may be subnormal. In *heat stroke* the heat-regulating mechanism is overwhelmed, and the temperature may rise 10° or more. One case is on record in which the temperature reached 117° F. It should be noted that the rectal temperature may be much higher than the temperature in the mouth or the axilla.

Heat stroke may be caused by direct exposure to the sun, the condition known as sun stroke. The ultra-violet rays have no relation to the condition. But the same effect is produced by exposure to any great heat, especially when combined with marked humidity. Men in steel works, engine rooms, etc., often suffer in this way.

In the condition of heat stroke the patient may die with startling suddenness. He may fall down unconscious, a condition known as *heat apoplexy*, not uncommon in soldiers on forced marches in tropical countries. Even in the less sudden cases the patient may soon become unconscious. In heat exhaustion the skin may be moist, but in heat stroke it is usually dry and burning; the patient appears unable to perspire. The temperature may rise to great heights, but not in every case.

The *pathological lesions* are very indefinite. The chief autopsy findings are petechial hemorrhages in the skin and mucous membranes, hyperemia or actual hemorrhages in the brain, cerebral and pulmonary edema, enlargement of the spleen, and cloudy swelling of the liver, kidneys and heart. The water content of the brain is high. Patients with a temperature of 110° F. have recovered, but such a temperature can only be endured for a short time, for it has been shown experimentally that a temperature of 108° F. if long continued will cause coagulation of the globulin of the nerve cells. After death from heat stroke the body shows very rapid and very marked rigor mortis. Postmortem decomposition also sets in very quickly.

## COLD

**Death from Freezing.**—When a person inadequately protected is exposed to severe and long-continued cold, and the blood is driven from the surface into the interior of the body. The temperature gradually falls, metabolism slows down, and the patient is overcome by the irresistible and fatal desire to sleep, so well known to mountaineers caught by bad weather at high altitudes. When the temperature reaches 70° F. the heart stops.

**Frostbite.**—The action of extreme cold on exposed parts of the body (nose, ears, hands, and even feet), especially when combined with the rapid loss of heat caused by wind, is to produce frostbite. As in the case of burns there are various degrees. In mild frostbite the part, which is at first white and bloodless, becomes red, swollen, and very painful during the process of thawing out. In more marked cases there is some necrosis of the epidermis, with formation of blisters and subsequent desquamation. In the severe cases there is necrosis of the entire part and gangrene. If the cold is sufficiently great the fluid of the cells is crystallized, and the cells are torn to pieces by the ice crystals. In ordinary cases the major factor in the production of the gangrene is the ischemia due to extreme contraction of the blood-vessels, together with damage to the capillaries with the formation of hyaline thrombi.

An important element in the production of ischemia and anoxia is the process of *stasis*, which occurs quite early in frostbite (Kreyberg). As a result of severe injury to the vessel wall there is exudation of the fluid elements of the blood, so that the red cells become agglutinated into a jelly-like column which blocks the lumen effectively with resulting necrosis. The process is reversible if treatment be not delayed too long, even though the tissues have been frozen solid. The word *stasis* is here used in the Continental sense, rather than in its usual connotation of slowing of the blood stream.

High altitude frostbite in aviators presents a special problem. In an airplane at great altitude the face can be exposed to severe cold for several hours, but under similar conditions the fingers suffer to such an extent that gangrene may result. Intense reflex vasospasm of the peripheral arterioles causes ischemia and local anoxia. The constriction, which is almost instantaneous, occurs chiefly at the terminal end of the arterioles. This is followed by damage to the endothelium of the terminal capillary loops, with increased permeability of the loops or thrombosis at the arteriolar-capillary junction. If extravasation of fluid occurs before thrombosis the hand may become dropsical owing to accumulation of fluid between dermis and epidermis, or blistering may occur. In cases where amputation of the fingers has been necessary later the arteries may show a remarkable fibrous thickening of the intima apparently unrelated to previous thrombosis.

## LIGHT

Light is a form of energy and may act as an irritant just as does heat. It is made up of vibrations of very varying wave length. The shorter the wave

length the less is the penetrating power and the more are the rays arrested in the skin where they excite irritation. The rays beyond the short wave end of the visible spectrum (ultra-violet) create most irritation, while those beyond the long wave end (infra-red) are most penetrating and cause least irritation. Light may affect the body in the following ways:

1. Ultra-violet light produces the condition known as *sunburn*. This is independent of heat, for climbers on high snow peaks may be severely burned. The greater the altitude the more severe is the effect, for the short wave rays are no longer filtered out by a thick layer of atmosphere. Direct sunlight is not necessary, for the most severe burn I have ever experienced was on a day of thick mist in the Alps. The sensitivity of the skin varies much in different persons, depending on the amount of melanin it contains. Blondes burn much more readily than brunettes. The process of tanning (not burning) consists in a deposition of melanin in the more superficial layers.

The pathology of sunburn is the same as that of a first degree burn. There is intense hyperemia, a varying degree of edema, and some emigration of leucocytes. The edema may be so great as to raise the skin in blisters. Marked desquamation may follow the burn.

2. Those whose occupation exposes them for long periods to bright sunshine, *e. g.*, farmers and sailors past middle age, often develop thickened patches or *keratoses* on the skin of the face and the back of the hands. The importance of these keratoses is that not infrequently they form the starting-point of carcinoma.

Probably related to this condition is the rare but remarkably interesting disease known as *xeroderma pigmentosum*. This appears to be a congenital hypersensitiveness to the action of light. In young children following prolonged exposure to sunlight there appears patches of erythema which go on to pigmentation. These patches then become rough and scaly, warty elevations appear (keratoses), and many of these become cancerous, so that the disease is usually fatal before the twentieth year. Metastases are rare both in this disease and in carcinoma following senile keratoses. There may be several cases in one family, but it is limited either to the males or the females.

3. A *hypersensitiveness to light* may be present. In one of the rare inborn errors of metabolism, *hematoporphyria congenita*, hematoporphyrin is present in the blood and appears in the urine; the skin is hypersensitive to bright light, developing vesicles. The bones are pigmented. Even more remarkable is the sensitization which follows the experimental injection of hematoporphyrin. When an animal is treated in this way it becomes as sensitive to ordinary white light from which the ultra-violet rays are excluded by red glass as is a normal animal to ultra-violet rays. The hematoporphyrin appears to act as a sensitizer in the photographic sense. When the sensitized tissues are exposed to ordinary light there is a complete stasis in the vessels followed by necrosis. Exposure to intense light is followed by acute general effects. *i. e.*, excitement, convulsions, and death in the course of a short time.

4. Ultra-violet light exerts a *photochemical action on the lipoids of the skin*. The ergosterol of the skin seems to be activated by ultra-violet light and converted into vitamin D. Sunlight or the ultra-violet light from a mercury-vapor lamp is as efficacious in the treatment of a vitamin D deficiency disease like rickets as is the administration of cod-liver oil.

## ELECTRICITY

The passage of an electric current through the body may cause burns of varying severity or may result in death; the latter condition is known as electrocution.

The *local effects* are those of a burn. The current enters the body at one spot and leaves it at another. It is at these points where



resistance is encountered that evidence of the burn is most marked. At the point of exit the lesion is particularly severe, as in a gunshot wound, the tissues sometimes showing radiating tears. The point of exit is often on the feet, as the current leaves the body there to pass into the ground. The burn may be of any degree of severity. It usually does not look as bad as it really is. At first it is dry and bloodless, but in the course of thirty-six hours marked hyperemia and edema have developed. Little cavities may be found in the epidermis, supposed to be caused by the sudden generation of steam. A slough separates, and the ulcer thus formed is singularly slow to heal, usually taking two or three times as long as in the case of an ordinary burn.

The *general effects* resemble those of any severe burn. In fatal cases the viscera are congested, the serous membranes show petechial hemorrhages, the lungs are edematous, and the right ventricle is full of dark fluid blood. Death is probably due to respiratory rather than to cardiac failure, for the patient may sometimes be resuscitated by prolonged artificial respiration. The muscles are flaccid, although during life they may be in a state of severe tetanic spasm. There may be chromatolysis and degeneration of the nerve cells. The blood-vessels are severely injured for they serve as good conductors of the current, so that thrombosis and severe hemorrhages are common. In judicial electrocution the current is applied to the central nervous system and death is instantaneous, so that most of the above changes are not found.

*Lightning* produces the same results. There may be all kinds of skin wounds—puncture wounds, lacerations and bruises. Bands of scorched skin may pass from the point of entry (usually the head) down the body to the point of exit. The most characteristic feature is the so-called current markings or lightning figures, peculiar arborescent red lines on the skin which are probably caused by the current being split up in dendriform fashion within the body.

## ROENTGEN-RAYS AND RADIUM

The destructive effect of roentgen-rays and radium is identical, so that they may be considered together. The alpha rays and soft beta rays of radium are absorbed in the superficial layers and are therefore destructive to the skin; the hard beta rays and gamma rays penetrate readily and therefore are less likely to burn the skin. The alpha rays are the most potent agent known to science. They are 10,000 times more destructive than the gamma rays owing to the terrific impact of the alpha particle, and we shall see presently what happens when they exert their influence on the interior of the body. Fortunately they are very readily screened out; a thickness of 1 mm. of tissue is sufficient to stop them. Roentgen-ray burns were common in the early days before the importance of screening was understood; they are seldom seen now. The radiations act primarily on the nucleus of the cell, not on the cytoplasm. The normal cell is far more vul-

nerable during division than in the resting stage; the same is true of tumor cells.

Radiations may produce a burn of the skin, but this displays some very special features. The lesion does not appear at once, there being a latent period of about two weeks. The changes which then develop are of all degrees of severity. There may only be the usual hyperemia and swelling with falling-out of the hair. Blisters may form, and a necrotic slough may separate leaving an ulcer. The burned skin may become like parchment and may not separate for a considerable time. The burn may include the skin, the subcutaneous fat, and even the muscles. Healing is very slow, and scarring may go on for months, causing marked deformity. At any time fresh ulceration may develop in the affected area. Repair indeed is never complete. It has been well said that a healed roentgen-ray burn is not a cured roentgen-ray burn.

A rather different set of changes is seen as the result of frequent small doses. These frequently developed in the hands of radiologists before efficient screening was practised. Some of the features of roentgen-ray dermatitis are as follows: patches of atrophy in the skin; areas of hyperkeratosis which may come and go, and finally may develop into carcinoma; scaliness of the skin and painful cracks and fissures; brittleness and splitting of the nails; a dermatitis like xeroderma pigmentosum; the development of telangiectases in the skin. The fingers and hands may be lost.

These effects are due partly to the direct action of the radiations on the tissues, but are largely secondary to the all-important vascular changes. Microscopically there is the usual hyperemia and exudation of inflammation. In cases of long standing the epidermis shows marked signs of proliferation. Many of the cells are undergoing mitosis, and downgrowths of epithelial cells invade the corium. It is in these lesions that carcinoma is apt to develop. There may be an interval of some years between the last exposure and the development of carcinoma, but active processes are going on the whole time. Fibrosis of the corium is marked, and the new fibrous tissue may be extremely dense and acellular. Vascular changes are constant. The capillaries may be dilated and form telangiectases. In the arteries, and to a lesser degree in the veins, there is a remarkable thickening of the subendothelial coat producing extreme narrowing of the lumen and in many cases complete occlusion. It is for this reason that proper healing is impossible and that subsequent breaking-down of the scar is so frequent. Thrombosis is common in the narrowed vessels.

**Industrial Hazards.**—If radio-active substances in the form of salts gain entrance to the body there may be terrible consequences. These substances may be present in infinitesimal amounts, but as they are stored within the body, particularly in bones, their action is cumulative and unceasing. Roentgen-ray pictures have been taken using the bones of a body exhumed five years

after death, so rich were they still in radio-active material. Workers with radio-active paints have been exposed to this hazard. Girls employed in painting luminous dials of watches used to lick the brushes many times a day. In this way the radio-active material gained entrance to the body, and the unscreened alpha rays, which are really particles of matter rather than true waves, were free to exert their destructive action. Being stored in the bones they set up a continual bombardment of the bone-marrow, with the result that a profound and fatal leucopenic anemia was produced. In addition both the upper and lower jaws developed destructive lesions like those of phosphorus poisoning, due as in that disease to bacterial infection from the mouth being superadded to a specific osteitis. Once the alpha particles have been introduced into the body it is impossible ever to get rid of them. For this reason the matter is one of great importance from the viewpoint of public health.

## TRAUMA

The commonest of physical irritants is trauma, so common indeed that were the subject to be considered fully it would necessitate a discussion of injuries of every organ in the body. A few of its effects may be considered here. The most readily recognized result of trauma is *bruising*, due to tearing of minute vessels in the subcutaneous or deeper tissues. The resulting extravasation of blood may be diffuse or localized depending on the looseness or density of the tissue. The kaleidoscopic procession of colors in bruising of the tissues is well known; first red, then bluish-green, and finally fading away into yellow, as the hemoglobin is converted into bilirubin and then gradually removed. Signs of inflammation are also present especially when the injury is severe, due to liberation of histamine by the lacerated tissues. If there is great destruction of tissue, the histamine passing into the circulation may produce a condition of shock. There may be *rupture of viscera* such as liver, spleen or bowel. It must be noted that serious internal injuries may be produced without bruising of the skin, even though the trauma be quite severe. Traumatic head injuries, with or without fracture of the skull, are considered in Chapter XXXI.

The relation of trauma to *infection* is of importance, quite apart from the introduction of bacteria from without. The part which trauma plays in the production of acute inflammation of bone (osteomyelitis) is well recognized. Here the injury, perhaps by causing small hemorrhages, gives pyogenic bacteria circulating in the blood the chance to become colonized in the bone and form an abscess. Tuberculous lesions of bones and joints may be caused in the same way. Mechanical injury in a syphilitic person may be followed by the development of a gumma in the traumatized area. Chronic osteoarthritis bears a very direct relation to trauma, often frequently repeated and minor in degree, but here the lesion is not due to infection but to injury to the articular surface.

Many other instances of the effect of trauma will be encountered in the sections dealing with Special Pathology; the examples given above are merely chosen as characteristic of the varied reactions which it may produce in the tissues.

## INCREASED ATMOSPHERIC PRESSURE

*Caisson disease* or diver's palsy is a result of a sudden alteration in the atmospheric pressure. A caisson is a cylinder containing air under high pressure used for sinking piers in the construction of bridges. Caisson workers, tunnel workers (under rivers), and divers are subjected to high air pressures. If they are "decompressed" too quickly or return to a normal atmosphere too suddenly they develop headache, vertigo, dyspnea, pains all over the body called "the bends," and it may be paralysis. While the person is under high pressure a large amount of air, particularly nitrogen, is dissolved in the blood plasma. As the result of sudden decompression this gas is released as bubbles in the blood, and these form emboli particularly in the brain and spinal cord. Numerous small infarcts of the central nervous system are produced in this way and are responsible for most of the symptoms. Bubbles of gas may also be liberated in the nervous tissue and cause disintegration.

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## CHAPTER XIII

### INJURIES CAUSED BY CHEMICAL POISONS

THE subject of the action of chemical poisons on the body is a very large one, and is adequately treated in textbooks of toxicology and forensic medicine. For this reason many textbooks of pathology make no reference to the subject. But the medical practitioner may at any time have to perform an autopsy on a case of suspected poisoning, and it is desirable that he be familiar with the pathological findings caused by some of the more common poisons and the precautions which should be observed in collecting the material for chemical analysis.

Poisoning may be suicidal, homicidal or accidental. In a case of suspected poisoning which may assume medico-legal importance extreme care must be taken in performing the autopsy. The external appearances should be noted. Everything should be recorded in writing and nothing left to the memory. The stomach and bowel must be kept. When there is a question of diffusible toxins such as arsenic and strychnine, it is well to keep all the internal organs and much of the muscles. These various specimens are sent to the chemist for chemical analysis. They must be put into clean glass jars, which are then stoppered, sealed, and labelled. No preservative of any kind should be added.

In the description which follows only the commoner and every-day exogenous poisons are discussed. The endogenous poisons produced as the result of abnormal metabolism and bacterial poisons (toxins) are not considered.

**Corrosive Acids.**—The strong acids most likely to be taken for suicidal purposes are sulphuric, nitric, and hydrochloric. They are similar in action, and produce burns not only in the stomach, but also in the mouth, pharynx, and esophagus. The lesions of the lips must not be overlooked. The stomach is contracted as the result of irritation and thrown into folds. Patches of necrosis are scattered over the folds, and if the patient lives long enough the slough separates and leaves a raw surface. Similar changes are seen with all corrosive poisons. The acids vary as regards the color of the burns. With sulphuric acid the burnt tissue is brownish-red or black, with nitric acid it is yellow, and with hydrochloric acid white. The microscopic appearance is one of necrotic tissue on the surface with intense inflammation of the surrounding tissue. The acid removes water from the cells and dissolves epithelium and connective tissue. Nitric acid poisoning is common in munition works where smokeless powder is made from nitrocellulose obtained by treating cotton with strong nitric acid. If the fumes of the acid are inhaled severe inflammation of the larynx and trachea is produced.

**Caustic Alkalis.**—The strong alkalis (caustic soda, caustic potash, and lime) are also corrosive in their action. They dehydrate the cells and saponify the fats. The common form of alkali poisoning is by commercial lye taken either

for suicidal purposes or accidentally by children. The lesions are similar to those of the corrosive acids. There is severe burning of the lips, mouth, throat, esophagus, and stomach, with acute inflammation and softening of tissue. Should the patient recover, cicatricial stricture of the esophagus often develops and sometimes stricture of the pylorus.

**Carbolic Acid.**—Strong carbolic acid is so easily obtained that it is commonly used for suicidal purposes. The picture differs in several ways from that of poisoning by other strong acids. The burns on the lips and in the mouth, throat, and stomach have a peculiar opaque, dead-white appearance. The stomach is contracted, and the dead patches are seen on the summit of the folds. Phenol is not a corrosive acid. It is an excellent fixative, so that the tissue instead of being destroyed is perfectly fixed. It follows that although the gross appearance is so abnormal, the microscopic picture is actually more normal than usual, because the customary postmortem changes in the stomach are absent. If the patient survives for some time the dead tissue will become detached with separation of a slough. The effect of dilute carbolic acid is rather different. The tissue is not killed and fixed so completely, and an intense hemorrhagic inflammation is the result of the irritation. When the stomach is opened in carbolic acid poisoning the characteristic color of phenol can be recognized.

**Corrosive Sublimate.**—This substance is also a favorite with suicides. When bichloride of mercury is taken in the form of a concentrated solution and in large quantity it fixes the tissue in the same way as does phenol. Grayish-white patches of coagulation necrosis are surrounded by an area of intense inflammation. When, as often happens, tablets are swallowed, they produce severe local necrosis with deep ulceration. After a few days a second set of symptoms develops connected with the colon and the kidney. By whatever route mercury enters the body, through the skin and mucous membrane (vaginal douches) as well as by the mouth, it is excreted into the large bowel, where it produces an intense hemorrhagic colitis. It is also excreted by the kidney. The cells of the convoluted tubules show extensive necrosis, and there is marked suppression of urine and sometimes anuria. In the course of a week or less there occurs an "acute calcification" of the renal lesion, calcium salts being deposited in the masses of necrotic cells, many of which lie free in the lumen of the tubules. This very rapid calcification is a remarkable phenomenon which it is difficult to explain.

**Arsenic.**—Arsenical poisoning may be acute or chronic. The acute form is usually suicidal, Paris green, rat poison, etc., being easily obtained. Chronic arsenical poisoning may be homicidal. Many of the famous murders in history have been accomplished by the continued administration of small doses of arsenic. Fashions change, however, and more violent methods are now in vogue. Arsenic is an intense irritant, so that in acute poisoning there is severe hemorrhagic inflammation of the entire gastro-intestinal canal. The poison is excreted into the bowel, giving an enteritis as well as a colitis. Paris green or crystals of arsenic may be seen in the folds of the stomach. In chronic poisoning the lesions are mainly in the skin and the nervous system. There is pigmentation and extreme keratinization of the skin. The nervous changes are mental disorders and paralysis of the peripheral nerves due to neuritis. Arsenical poisoning may be the result of the careless administration of arsphenamine and other arsenical preparations. In these cases the chief changes are optic atrophy with blindness and extensive necrosis of the liver. The latter lesion is often fatal.

**Phosphorus.**—This is likely to be taken in the form of rat poison or the phosphorus may be obtained from the heads of matches. Phosphorus poisoning may be acute or chronic. In the *acute form* there is a hemorrhagic inflammation of the stomach. The characteristic smell of phosphorus may be detected when the stomach is opened. After an interval of some days there is acute necrosis of the liver with a picture of acute yellow atrophy, accompanied by intense jaundice and widespread hemorrhages. Phosphorus is one of the most potent

causes of fatty degeneration, and this change is present in marked degree in the liver, kidneys, heart, and even the voluntary muscles. *Chronic poisoning* is due to exposure to phosphorus vapor, and is an occupational disease. Apart from fatty degeneration the chief lesion is necrosis of the jaws (phossy jaw) with destruction of bone and loss of the teeth. The process is dependent on bacterial infection, commencing round the roots of carious teeth. In this and other respects it closely resembles the lesion of industrial radium poisoning.

**Lead.**—Lead poisoning (plumbism) differs from those already described in being chronic in type; acute lead poisoning is of no importance. It is usually an occupational disease, the lead being inhaled in the form of dust or fumes or absorbed through the skin. White-lead workers and pottery workers are liable, and painters unless they wash their hands well before eating. A severe anemia develops, of which the characteristic feature is an extreme degree of basophilic granular degeneration (stippling) of the red cells. In no other disease is this change so marked. A blue line (lead line) of lead sulphide appears at the junction of the gum and the teeth, owing to the action of sulphuretted hydrogen on the lead. Constipation is a marked feature, and there may be painful colic. Peripheral neuritis affecting particularly the musculospiral and peroneal nerves may lead to drop-wrist and drop-foot. There may be depression, delirium, convulsions, and mental changes, with degenerative changes in the cerebral cortex like those of general paralysis. There appears to be some relation between chronic lead poisoning and gout on the one hand and the arteriosclerotic form of chronic nephritis on the other.

*Lead poisoning in children*, a fairly common but usually unrecognized disease, presents many points of special interest. It is often mistaken for poliomyelitis. The incidence is highest in infants and young children with erupting teeth, who put painted objects containing lead (yellow paint is specially dangerous) into their mouths. Many suffer from perversion of appetite (pica), and lick the paint off their cribs and the furniture. The child may drink water containing lead or inhale fumes from storage battery casings used in the stove for fuel. In Japan congenital plumbism is common, owing to the pregnant mother covering her face and neck with cosmetics containing lead. Gastro-intestinal symptoms (vomiting, colic, constipation) and anemia may be marked, but the most striking symptoms are those of lead encephalitis, *i. e.*, a change in the mental state, visual disturbances, convulsions and coma. The blood-pressure may be raised, there may be choked disc, and even separation of the cranial sutures. The actual cerebral lesions are merely minute hemorrhages and cellular infiltrations; the symptoms are caused by rapid increase of the intracranial pressure due to intense cerebral edema, as a result of which the brain is swollen, the convolutions flattened, and the medulla pressed into the foramen magnum. The cerebrospinal fluid pressure may be as high as 700 mm. of water (normal 120 mm.). Peripheral neuritis is rare. The lead line on the gums is seldom seen in children (no doubt owing to the healthy condition of the mouth) and stippling of the red cells may be absent. One of the most useful signs is a lead line in the bones in the roentgen-ray film; there are zones of increased density at the growing ends of the long bones, where lead is deposited in place of calcium. This line is rarely absent, even in mild cases.

Much of the lead is stored in the bones. Parathyroid extract, with its well-known effect on calcium metabolism, causes both calcium and lead to be mobilized, removed from the bones, and excreted in the urine. There is a corresponding rise in the blood calcium. Much of the lead can be rapidly removed in this way, but the remainder is firmly united to the bone and is only excreted slowly.

**Prussic Acid.**—Hydrocyanic acid and the cyanides are suitable for suicidal purposes because they are so rapidly fatal. The poison is not corrosive, but the gastric mucosa has a bright chestnut-brown color. The blood remains fluid. The poison kills by acting on the nervous system and the heart, and there are no special postmortem lesions, but the characteristic peach-kernel smell can often be detected when the stomach is opened.

**Alkaloids.**—The poisonous alkaloids such as opium (morphine), strychnine, cocaine, atropine, etc., produce no characteristic postmortem changes. Their detection therefore depends on chemical analysis.

**Alcohol.**—**Methyl Alcohol.**—Methyl alcohol, so common an ingredient in bootleg liquor, and used for "denaturing" ethyl alcohol, is highly toxic. The deaths which follow the drinking of "canned heat," etc., are due to methyl alcohol poisoning. In these cases there is nothing to be found at autopsy apart from severe gastritis and a smell of alcohol in the stomach, lungs, and brain. After a few hours this smell may disappear. If the patient recovers he may be blind from optic atrophy.

**Ethyl Alcohol.**—Ethyl alcohol may also produce death in a few hours if taken in sufficient quantity and concentration. The postmortem findings are the same as those of acute methyl alcohol poisoning. If the patient has lived a few days there may be marked edema of the brain. The effects of *chronic alcoholism* are very debatable. Undoubtedly resistance to infection is lowered, so that the patient may die of pneumonia, etc. Many degenerative lesions are attributed to chronic alcoholism. Among these are cirrhosis of the liver, chronic gastritis, chronic nephritis, and arteriosclerosis. The direct relation of any of these to alcohol is more than doubtful, but it may act as a contributory cause. Chronic alcoholics undoubtedly show a marked fatty degeneration of the liver, a lesser degree of fatty change in the heart and kidneys, atrophy of the seminiferous tubules in the testicle, and cerebral edema or "wet brain."

**Chloroform.**—A person may die while under chloroform anesthesia, or may die an acute death after swallowing the liquid. In these cases there are no characteristic postmortem changes apart from the odor of chloroform. The patient may die later of "delayed chloroform poisoning," and autopsy will reveal profound fatty degeneration of the liver, heart, and kidneys. Death is due to interference with the function of these organs, particularly the liver.

**Carbon Monoxide.**—In carbon monoxide poisoning the gas may come from illuminating gas, from stoves or furnaces, from the products of explosions in coal mines, but the most important source at the present day is the exhaust from automobiles. A car running in a small closed garage will generate enough gas in a few minutes to kill a person. Garage workers breathing a smaller concentration may suffer from a train of symptoms such as headache, vertigo, and weakness. Traffic policemen directing very heavy automobile traffic in large cities may suffer from minor forms of poisoning.

The carbon monoxide combines with the hemoglobin, replacing the oxygen and forming carboxyhemoglobin. The patient therefore dies of asphyxia. But in addition there seems to be a direct poisonous action on the vital centers, for the patient may become unconscious with extraordinary suddenness. It is this rapidity of action which constitutes the great danger of the gas in concentrated form. As the carboxyhemoglobin is of a bright color, the face, the blood, and the viscera assume a cherry-red. This and a markedly fluid blood constitute the chief postmortem changes. If the patient should live for some days a remarkable bilateral necrosis is found in the lenticular nucleus of the brain, being most marked in or confined to the globus pallidus. It is the iron of the hemoglobin with which the carbon monoxide unites. It is therefore possible that the gas may combine with the iron in the walls of the vessels of the globus pallidus, the iron content being higher than in any other vessels of the body. The necrosis is probably due to ischemia, which in turn is probably caused by thrombosis of these small vessels.

**Botulism.**—Although botulism is caused by a bacterial poison it may for convenience be considered here. The toxin is formed by the *Bacillus botulinus* (*botulus*, a sausage) which grows in spoiled sausages, preserved meat, canned vegetables, fruit, ripe olives, etc., especially those preserved by home canning in which the temperature employed is insufficient to insure sterilization. Thus the poison is ingested ready-made, and is not manufactured inside the body. It is easily destroyed by heat, so that cooking renders the food harmless. It is extremely powerful, and even small amounts may cause death.



Like the tetanus toxin it does not act at the point of absorption, for there is never any evidence of gastro-intestinal irritation. The symptoms are entirely cerebral, and are apt to be mistaken for those of epidemic encephalitis. Indeed, the first cases of the latter disease which appeared in England were thought to be examples of botulism. The most characteristic symptoms are ophthalmoplegias (squint, double vision), ptosis, and difficulty in swallowing and in speech. All of these are due to cranial nerve palsies. The postmortem findings are merely those of toxemia—cloudy swelling, petechial hemorrhages, etc.

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## CHAPTER XIV

### HEREDITY AND CONSTITUTION IN DISEASE

#### HEREDITY IN DISEASE

IN the causation of disease two great factors always demand consideration; these are environment and heredity. So far we have been concerned for the most part with the environmental diseases, those caused by bacterial, animal parasites, trauma, physical irritants, chemical poisons, etc. For the last sixty years and more, medicine has concerned itself with these extrinsic agencies which are more readily studied and for which more can be done than in the case of hereditary defects of the germ plasm. Far reaching and profound observations have been made in the past, above all by the Austrian monk Gregor Mendel in 1866, but the modern study of heredity and the explanation of the phenomena observed by Mendel date from the beginning of the present century with the rediscovery of his principle of segregation in 1900. This study has served to show, were the proof needed, that men are not created free and equal, but handicapped from the beginning.

There are two great classes of cells in animals and plants: the somatic or body cells and the germ cells. The body cells merely form a temporary shelter and covering for the germ cells. The germ plasma, as Weismann pointed out, is immortal though the body which shelters it must die. At an early period of development the cells which are to form the future germ cells are set apart, and take no part in body building. In *Ascaris* this occurs after the first division of the fertilized ovum (zygote), but in man it is delayed to a much later stage. The germ plasm resides in the nucleus, and it was Weismann who first identified it with the chromatin network.

**The Inheritance of Disease.**—We have seen that unit characters may be transmitted from parents to offspring, and that their characters, depending on whether they are dominant or recessive, will appear in the first or second generation *provided the breeding is controlled*. In addition to such characters as color, shape, size, fertility, vigor, length of life, etc., definite defects may also be transmitted, and these constitute hereditary disease in man. It is at once evident that the study of these defects is a very different matter from the investigation of the mode of transmission in peas and guinea-pigs, for in the case of man breeding is a matter of chance beyond control. Many of the hereditary diseases are relatively rare. For these reasons there has been a tendency on the part of the medical profession to

minimize the importance of heredity and to exalt that of environment. There is a growing feeling, however, that many of the commoner degenerative conditions of middle life, such as arteriosclerosis, may have their genetic representation in the germ plasm.

A distinction is sometimes drawn between *familial* and *hereditary* disease. This distinction is entirely imaginary, for familial diseases are always hereditary. When both parents must transmit the defect before it becomes recognizable we have the so-called familial cases, but this is merely an example of a recessive character. The parents need not and generally do not exhibit the defect themselves, as is evident to anyone familiar with the principles of genetics. A "familial disease" is one in which the pathological character is recessive, a "hereditary disease" is one in which it is dominant. A recessive character may be transmitted indefinitely in the germ plasm without coming to light until it meets a similar recessive from another strain. Disease factors in man are generally dominant, but they may be recessive or sex-linked. A disease, *e. g.*, diabetes mellitus, may in one family appear to be hereditary and in another familial, depending on the distribution of the genes for diabetes in the chromosomes. A *congenital* defect is one which is present at birth, although it may only develop later to a sufficient degree to be detected clinically, *e. g.*, congenital cystic kidney, congenital cerebral aneurism. This defect may be hereditary, but frequently it is acquired *in utero*; congenital syphilis, for instance, should not be called hereditary syphilis, for it is not transmitted by the germ plasm.

**Simple Dominant Inheritance.**—This is the simplest type to recognize. Each affected individual has an affected parent and grandparent. The heredity is not sex-linked. Examples are brachydactyly (short fingers and toes), multiple cartilaginous exostoses, progressive pseudohypertrophic polyneuritis, Huntington's chorea, multiple polyposis of colon and rectum, sickle-cell anemia, diabetes insipidus and angioneurotic edema. All of these diseases are commoner in the male, and are often transmitted by the male. In one family there were 23 cases of diabetes insipidus among 91 members in 4 generations.

**Simple Recessive Inheritance.**—It is much more difficult to recognize a simple recessive heredity from the family history than a simple dominant. The factor must be present in a duplex condition from both parents in order that the individual may show it. The affected individual results from the mating of two parents who are outwardly normal, but are really heterozygotes or hybrid carriers ( $DR + DR = DD$ ,  $2 DR$  and  $RR$ ,  $RR$  being the only one to exhibit the disease). Normality is nearly always dominant to defectiveness. That is one of the blessings of a recessive character. A lethal gene may be paired with a normal (dominant) gene, but its possessor goes through life unconscious of the fact that genetically he is half dead. The factor for the defect may be handed down through many generations of normals, until a chance mating of two heterozygotes occurs. It is inbreeding which is likely to bring out a recessive character. It is of

importance, however, to realize that inbreeding (consanguineous marriages as between cousins) is only bad when hidden harmful characters exist in the stock. It is harmless and even beneficial when the hereditary constitution of the stock is sound. Examples in man: amaurotic family idiocy, retinitis pigmentosa, Friedreich's ataxia, alkaptonuria, xeroderma pigmentosum.

**Sex-linked Inheritance.**—Theoretically the character carried by the sex or X chromosome may be dominant or recessive. In practice no examples of dominant inheritance are known. Recessive sex-linked inheritance is very readily recognized, in distinction to the simple recessive autosomal form. The male, who has only one (affected) X chromosome, will exhibit the defect. The female has also one affected X chromosome, but it is held recessive by the other normal X chromosome. She is therefore a heterozygote or carrier. If by rare chance she should inherit two affected X chromosomes, one from each parent, she would probably show the defect. The carrier female transmits the defect to half her sons, and half her daughters will be carriers (heterozygotes). If both parents are affected, all the offspring will be. The reason why, as a rule, only half the sons inherit the disease and half the daughters become carriers is that in the heterozygous female only one X chromosome carries the taint, and there is an even chance that this is the one which may be lost during maturation of the ovum. The criss-cross inheritance of the sex-linked diseases, the defect traveling by the route father → daughter → grandson is due entirely to the movement of the sex-determining chromosome. Important examples of sex-linked inheritance are hemophilia, color-blindness, night-blindness, and Leber's hereditary optic atrophy.

A very large number of diseases, for the most part rare, are now supposed to have their origin in some hereditary defect in the germ plasm, although, for reasons already discussed, the physician may find it impossible to establish the hereditary factor in an isolated case. A good idea of the number of these diseases can be obtained by consulting the list in Macklin's article in *Medicine*, 1935, **14**, 1, or in Crew's *Organic Inheritance in Man*. A few of these merit brief reference.

*Blood diseases* include hemophilia, pernicious anemia and sickle-cell anemia. Hemophilia, a perfect example of a sex-linked recessive character, has already been considered. Pernicious anemia usually gives little or no evidence of a hereditary tendency unless a very full family tree can be drawn up, but several cases of achylia gastrica may be found in the same family, and this condition undoubtedly precedes the onset of pernicious anemia. It looks as if the achylia were a hereditary character, the operation of some extraneous factor occasionally precipitating in such persons an attack of the disease. Sickle-cell anemia behaves as a dominant. Eo-sinophilia may be familial. I have studied two brothers, in one of whom the eosinophils averaged 80 per cent and in the other around 20 per cent. Hemorrhagic telangiectasis, a condition characterized by spontaneous bleeding from dilated vessels in the nose and mouth and the appearance of red spots in the skin commencing about the time of puberty, behaves as a dominant. One of the most striking examples of human heredity is afforded by the blood groups, the agglutinogens acting as dominants.

*Metabolic disorders* belonging to the group called by Garrod the inborn errors of metabolism are hereditary in origin. Members of this group are alkaptonuria and cystinuria. Diabetes insipidus is a dominant character, at least one parent also showing the defect. The lipoid storage diseases (Gaucher's disease, Niemann-Pick's disease, etc.), and abnormal glycogen accumulation (von Gierke's disease) likewise have a genetic basis. Heredity is usually strongly marked in gout.

The *skeleton* is often the site of hereditary defects. Multiple cartilaginous exostosis is also known as hereditary deforming chondrodysplasia, a name which announces the inherited nature of the defect. Brachydactyly, or short fingers, the first example of Mendelian inheritance demonstrated in man, is a simple dominant. The fingers have only two phalanges, the second and third being fused owing to absence of an epiphysis in the former. A similar type of defect in the hand has been transmitted from one of Henry the Sixth's nobles in the 15th century to descendants living at the present day; the recently exhumed skeleton of the original earl showed the same bony change. Fragilitas ossium, a condition characterized by multiple fractures and sometimes associated with blue sclerotics, may show a very marked familial tendency, nearly always dominant. Males and females are about equally affected, transmission taking place equally through both sexes.

The *nervous and neuro-muscular systems* furnish a large variety of hereditary diseases. Progressive muscular atrophy, pseudohypertrophic muscular dystrophy (dominant or recessive or sex-linked), Friedreich's ataxia (dominant or recessive), progressive lenticular degeneration (Wilson's disease), peroneal atrophy, amyotonia congenita, myotonia congenita and many others are familial in character due to inherited defects in the germ plasma. Muscular tremor may be markedly hereditary, and is usually dominant.

The *skin* and its appendages show a variety of inherited defects. Mention may be made here of baldness, which is markedly hereditary in character. It is much commoner in men than in women, being dominant in males, but recessive in females. The male may inherit it from father or mother, but the mother, being heterozygous, is not bald. Xeroderma pigmentosum (Kaposi's disease), a disease of the skin occurring in childhood and characterized by the occurrence of inflammation when exposed to the sun with subsequent development of multiple cutaneous carcinomata, is recessive in all cases. Von Recklinghausen's disease, or multiple neurofibromata, is always dominant, but in some cases pigmented areas take the place of tumors, so that the dominant character is apt to be overlooked.

*Eye diseases* constitute one of the largest groups and serve to fill the blind asylums. Chief among these may be mentioned retinitis pigmentosa and hereditary optic atrophy (Lever's disease), the latter offering an excellent example of a sex-linked disease, being confined to the male but transmitted through the female. Blue sclerotics is an ocular manifestation of a defect of connective tissues in general, including the bones (fragilitas ossium). The blue color is due to the underlying choroid shining through the thin sclerotic. The condition is a good example of a non-sex-linked defect. It is not transmitted by those not affected, it appears in both males and females, it is transmitted from fathers to sons and daughters and from mothers to sons and daughters. The defect is of course not carried in the sex chromosome. Color-blindness and some forms of night-blindness (the patient becoming blind at dusk owing to lack of the visual purple in the rods of the retina) are both sex-linked. Coloboma of the iris and its extreme form, known as aniridia or absence of the iris causing blindness, are markedly hereditary. Risley records an extraordinary and tragic family history in which one blind man had 13 children who were all blind, 61 blind grandchildren out of 63 and 39 great grandchildren out of 42, a total of 113 blind offspring out of 118. A strong argument for eugenics. Glioma of the retina (retinoblastoma), a neoplasm which is fatal unless removed early, often shows a marked hereditary tendency. In a family of 16, 10 died of this tumor. It is always recessive. There is a marked hereditary

tendency in all varieties of cataract, and in amaurotic family idiocy. Strabismus is dominant in some families, recessive in others.

*Mental diseases* are often due to a defect in the germ plasm. Dementia præcox offers a good example. Huntington's chorea is an example of a simple dominant autosomal character. One family from Long Island has furnished practically 1000 cases of this disease. Some types of feeble-mindedness are inherited as simple recessives. Matings of feeble-minded persons with each other gave only 6 normal children out of 482 from 144 such unions (Goddard). The 6 normals may have been a mistake, as in the case of two feeble-minded white parents who had 10 feeble-minded and 2 normal children, but the two normals were black! Amaurotic family idiocy and Mongolian idiocy are always recessive.

*Heredity in cancer* is a difficult matter to pass judgment on. It has already been discussed in connection with tumors, so it will only be touched on here. "In the question of human cancer heredity, all existing statistical evidence is valueless for any exact information on the subject" (Wells). People do not know what their grandparents and great aunts died of, and if they did, the diagnosis would be as often wrong as right. Moreover, an hereditary character may be transmitted through a son incapable of showing that character, *e. g.*, a bull is valuable because it comes of a famous milk-producing strain. A woman with cancer of the uterus may transmit that gene to her son, but it cannot manifest itself; it may be transmitted in the same way to a grandson, and the fatal character may finally appear in his daughter. In such a case it is natural that the heredity tendency should be completely lost sight of. One of the neoplasms in which the influence of heredity is best seen is polyposis of the rectum and colon with its marked tendency to become malignant. Dukes records the case of a man who died of rectal cancer at the age of forty-two years. He had 9 children, 7 of whom developed rectal cancer; 5 were already dead, 1 at the age of twenty-seven years. The disease also appeared in the next generation. It is impossible to believe that in such a case as this there was not some hereditary defect in the germ plasm which acted as a determiner for cancer of the rectum. A man and his wife had cancer of the stomach, and 6 of their 7 children died of the disease. The seventh was killed at the age of twenty-eight years in an accident. In the experimental work on mice the incidence of cancer, its site and its character were all influenced by heredity. It is worthy of note that the larval stage of *Drosophila* suffers from a sex-linked entodermal tumor, which kills one-quarter of the males and is transmitted by the unaffected females.

*Resistance to infection* forms an interesting and important group. The body may be resistant in two ways. The infecting agent may not be able to get a foothold, or after invasion has occurred the resistance may be sufficiently good to overcome the infection. Susceptibility, like immunity, can be transmitted as a genetic character. Raymond Pearl describes a family of 13 children, all of whom had had lobar pneumonia before the age of eighteen years, 1 twice and 1 three times; 7 of the 13 had died of the disease. No explanation was found in the environment. Hagedoorn-La Brand made an interesting accidental observation on the hereditary transmission of resistance. A colony of mice consisting of Japanese mice, large albinos and hybrids of these, was attacked by an epidemic staphylococcal infection. All the Japanese mice died, but none of the albinos. The important fact is that none of the hybrids (first generation) was affected, but in the second generation 1 out of 4 succumbed. Thus the resistance of the albinos depended on a single dominant genetic factor. Webster tested a colony of inbred mice against *Bacillus enteritidis* (mouse typhoid), and got a 37.4 per cent mortality. By breeding from the progeny of the mice which died early after exposure, he obtained a strain which was 85 per cent susceptible. He obtained a strain from the progeny of the mice which survived the infection, and found only 15 per cent of susceptibles.

*Twins* provide a singular opportunity to study the effect of heredity and constitution on disease. In the case of identical (monozygotic) twins, one serves as a control animal for the other. It is as if we were watching one individual leading two physical existences. Margolis and Eisenstein give the following examples, of disease developing more or less simultaneously in both twins (1) Tumors. Twin developed retinoblastoma of the left eye within a few months of each other. Cancer of the right testicle appeared in both at the same time. (2) Nervous and mental disease. Dementia præcox, paranoia, and other mental disorders have developed at the same time. (3) Non-infectious systemic disease. At the age of sixty twin brothers developed diabetes characterized by the same set of symptoms, and both died within a few months of each other. Twin sisters in New York and San Francisco developed diabetes at the age of fifty-two and died within a short time of each other. Other diseases which have developed simultaneously in twins are lymphatic leukemia, nephritis, asthma, bronchiectasis, cataract, and Hodgkin's disease. (4) Infections. Twin sisters developed tuberculosis of the right kidney within seven months of each other. Many other similar examples could be given illustrating the profound importance which origin from a common germ plasm has on the development of disease.

### CONSTITUTION IN DISEASE

The subject of constitution is bound up with that of heredity. It has become the custom rather to smile at our medical forefathers when they talk in their writings of the weak constitution of the patient, but the central doctrine of Greek medicine was that of temperaments and constitutions, and the conceptions of Hippocrates are worthy of consideration even at the present day. Constitution, according to Draper, whose monograph on the subject should be consulted, is "that aggregate of hereditarial characters, influenced more or less by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of environment." John Hunter, Addison, and other great clinical observers of that period believed firmly that the habitus or physical form of the individual bears an important relationship to disease. This physical form is the anatomical aspect of constitution, and although by no means the only aspect it is the one which has been most carefully studied and the only one which will be considered here. "The anatomic features of an individual form one of a set of basic unit characters, predetermined by heredity, and influenced to some extent by environment, which together make up the constitution" (Draper). The anatomical aspect is related to the physiological, psychological and immunological aspects, and it was a recognition of this fact which formed the basis of the marvellous unconscious skill of the older physicians. The three basic elements of the disease problem are Man, the lesion, and the environmental stress, and we

are so much engaged with the two latter that the first is apt to be forgotten.

The capacity of an individual to react to the environmental stress is a constitutional quality, just as specific as body size and capable of being transmitted to his offspring. Longevity, which is the result and expression of a good constitution, is certainly inherited; everyone knows of families, the majority of whose members reach the late seventies or eighties, no matter what kind of life they may have led. We have already seen that this is the case with resistance to infection. Sex, which is considered below, has a profound influence on disease reactions, and this is determined by the presence or absence of an extra chromosome. In some way this must be linked with the commonness of gall-bladder disease and the comparative rarity of chronic peptic ulcer in the female. Size of body has been shown in animals to be a unit character. The entire skeleton may be altered by a defect in a single gene, and the person may be a giant or a dwarf. In this instance the determiner appears to act through an endocrine gland (pituitary). Race may play a part in predisposition to a disease. Thus certain diseases are peculiar to the Hebrew race. Amaurotic family idiocy is practically confined to Jewish children, while Gaucher's disease and Niemann-Pick's disease are much commoner in these children; Buerger's disease, diabetes mellitus, and pentosuria are commoner among Jews.

The *habitus* or general build of the body is a resultant of a combination of height and weight. On this basis it is possible to divide persons into the sthenic and asthenic groups. The *sthenic* individual is short and stout, with a wide costal angle and deep chest, inclined to be florid, of cheerful sanguine disposition, liable to gall-bladder disease, arterial hypertension and likely to die of arteriosclerosis, apoplexy or coronary occlusion owing to defects in his germ plasma at the time of conception. The *asthenic* individual is tall and thin, with a narrow costal angle, a pallid countenance, easily fatigued and inclined to be melancholy; he has a long, drooping stomach which empties poorly and intestines which sag, so that his melancholy may be aggravated by dyspepsia and constipation. He is a likely subject for peptic ulcer. He seldom has heart or arterial disease and is likely to be long-lived if he escapes tuberculosis in youth. The gall-stone man seldom has ulcer; the ulcer man seldom has gall stones. The pages of Shakespeare and Dickens are filled with immortal characterizations of these types.

**The Influence of Sex.**—The question of sex has already been considered in connection with sex determination and the sex-linked inheritance of disease. We have now to consider sex from the standpoint of human constitution, *i. e.*, the manner in which it influences the reaction of the individual to the stress of environment. In such a discussion the organs peculiar to either sex must be excluded, only those common to both being considered. When this is done the surprising fact emerges that very few serious organic diseases are commoner



in the female. Most diseases of the gastro-intestinal tract, respiratory tract, bloodvessels, heart, bones, joints and urinary tract are commoner in males than in females. Some diseases such as thromboangiitis obliterans are almost confined to the male, while others such as angina pectoris, coronary occlusion, peripheral arteriosclerosis, pernicious anemia, leukemia, lymphosarcoma, etc., are more frequent in that sex. The gall-bladder is a notable exception to the general rule, and to a lesser degree mitral stenosis. Functional disorders, on the other hand, such as Raynaud's disease, hypertension, migraine, hysteria and chronic nervous exhaustion are commoner in the female. There is a higher mortality for the male throughout all the periods of life. This cannot be explained away, as is commonly done, by reference to overwork, industrial hazards, abuse of alcohol and tobacco, venery, etc., for the difference in the sex mortality is most striking in intra-uterine life and during the first few years of childhood. There appears to be an inherent weakness in the male, a sex-linked inferiority, so that by comparison with the female he is a weakling at all periods of life from conception to death. This holds true throughout the animal kingdom, the males being shorter-lived. As Allen remarks, the price of maleness is weakness, and woman is far from being "the weaker vessel." Only a few organic diseases, such as those of the gall-bladder and thyroid, are commoner in females.

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## PART II

### SPECIAL PATHOLOGY

#### CHAPTER XV

#### THE HEART

**Descriptive Outline.**—In describing the gross appearance of the heart one must consider the pericardium, pericardial cavity, the size and weight of the heart, the myocardium, auricles, ventricles, endocardium, valves (cusps), valvular openings, and coronary arteries. The *pericardium* is smooth, shiny, thin and translucent. There is a varying amount of subpericardial fat. The *pericardial cavity* contains from  $\frac{1}{2}$  to 1 ounce (10 to 30 cc.) of clear, straw-colored, serous fluid. The *size* can only be learned by frequent observation of the normal. It may be increased or diminished in disease. The average *weight* is 300 grams in the male, 250 grams in the female, but these figures will be considerably exceeded in a big muscular laborer or reduced in a tiny fragile woman. The weight is largely dependent on the thickness of the left ventricle, and varies directly with the arterial blood-pressure, of which it is a fairly reliable indication. The *myocardium* has the reddish-brown color of voluntary muscle, and a consistence which may be increased or diminished in disease. To *open the heart* begin with the right auricle, passing the scissors through the mouths of the superior and inferior vena cava, and follow the direction of the blood flow into the right ventricle, left auricle, left ventricle, and aorta. The *cavities* of the auricles and ventricles are noted for dilatation and their walls for hypertrophy. The *wall of the right ventricle* is about 5 mm. thick, that of the *left ventricle* 10 to 15 mm. The *endocardium* lining the cavities is smooth, shiny and translucent so that the underlying muscle can be seen, but frequently the lining of the left auricle is thickened, white and opaque. The *valve cusps* should be as thin and smooth as fine silk. The commissures of the aortic valve, *i. e.*, the points where the cusps are joined together, have no appreciable thickness; any widening of these commissures is an indication of disease. As regards the *valvular openings*, the mitral should admit two fingers (two cusps) and measure about 7.5 cm. in circumference; the tricuspid should admit three fingers (three cusps) and measure about 10 cm. in circumference. The *chordæ tendinæ* attached to the mitral valve are slender fibers which may become thickened and shortened. Finally, the *coronary arteries* are opened and inspected.

The heart consists of three main anatomical elements, the myocardium, the pericardium and the valves. Any or all of these may be the seat of organic disease. It must be remembered, however, that no organ is influenced to so marked a degree by nervous stimuli and what are commonly referred to as the emotions. As my colleague, Dr. Allan Walters, has pointed out, the simple everyday words of our language testify to the truth of this statement. We say that a person is heavy-hearted, hard-hearted, heartless, good-hearted, that his heart

aches with loneliness, flutters with alarm or stops with fear. Although cardiac symptoms may, therefore, have an emotional rather than an organic basis, we are concerned in this place primarily with structural changes.

### LESIONS OF THE VALVES

**Rheumatic Disease of the Heart.**—The heart is a pump, and as impairment of the valves of a pump will wreck its efficiency it is natural that attention should have been focussed on rheumatic disease of the valves (endocarditis). Rheumatism, however, is a pancarditis, an infection of the fibrous tissue of all parts of the heart (endocardium, myocardium, and pericardium), nor does the aorta escape.

The bacteriology and the general pathology of rheumatic fever have already been discussed in Chapter VII. It was there pointed out that the disease was an infection of the fibrous tissues of the body accompanied by the formation of a characteristic pathological lesion, the Aschoff nodule. This lesion is seen in most typical forms in the myocardium, but lesions sufficiently distinctive to be recognized occur in the cardiac valves, pericardium, synovial membrane, periarticular tissues, skin, etc. The damage is primarily to the supporting tissues, *i. e.*, collagen and elastic tissue. The first change is fibrinoid degeneration, followed later by actual necrosis. Exudation characterizes the early stages, proliferation the later and finally fibrosis. In the valves this leads to postinflammatory adhesions and contraction with accompanying stenosis or incompetence, in the myocardium it leads to weakness, and in the pericardium to adhesions. Rheumatism may lick the joints, especially in children, but it certainly bites the whole heart. Rheumatic heart disease is predominantly a disease of childhood, youth and early adult life. Probably more than 70 per cent of the cases occur before the age of twenty, the peak of onset being between the ages of five and ten.

**Valvular Lesions.**—By far the commonest valvular defect resulting from rheumatic fever is mitral stenosis. In the aortic valve there may be a moderate degree of incompetence (never so complete as in the syphilitic form) or, more rarely, stenosis which years later may take the form of so-called calcific sclerosis. The lesions of the valves on the left side are more extreme owing to the greater strain on those valves. The mitral valve suffers more frequently in women, the aortic valve in men. The reason for this is not known. If the valve ring, to which the cusps are attached and which is really the proximal part of the valve, be examined microscopically, all four valves will be found to be involved in most cases (Gross and Friedberg). In the mitral and aortic valves the process is usually progressive, less often in the tricuspid, and least in the pulmonary, so that in the two latter gross lesions are correspondingly rare. Infection seems to begin in the valve rings, although the primary focus in the case of the mitral is probably the wall of the auricle, and in the case of the aortic the root of the aorta. Infection may readily spread between the mitral, aortic and tricuspid

rings by way of the intervalvular fibrosa and the septum fibrosum. The close proximity of a fibrous pericardial wedge to most of the valve rings favors spread of infection from pericardium to valves. It must be understood that the rings may show microscopic lesions although the cusps remain free.

The essential lesion in rheumatic endocarditis is the presence of rheumatic nodules in the endocardium of the valves. This leads to a diffuse thickening of the cusps. An additional although not essential feature is the formation of rheumatic vegetations. These are tiny bead-like warty (verruccose) nodules arranged in a row along the margin of contact (not the free margin) of the cusps, and therefore on their proximal aspect. (Fig. 157.) They consist of platelet thrombi deposited on the raw surface which results from trauma to the endothelium of the valve along the line of contact. This trauma is greatest on the left side of the heart where pressure is highest, but when mitral incompetence develops the pressure on the right side also rises, so that if the



FIG. 157.—Rheumatic endocarditis. A bead-like row of vegetations runs along the line of contact of a cusp of the mitral valve.

infection recurs vegetations will be formed on the tricuspid valve. They are firm and adherent, so that they are not detached by the heart's action. For this reason embolic phenomena are not seen in rheumatic endocarditis. When they are rubbed off, the underlying surface is raw. The mural endocardium may also be involved. On the posterior wall of the left auricle just above the mitral valve there may be a rough thickened patch which becomes scarred later, and may form a nidus for *Streptococcus viridans*. This is often called the *MacCallum patch*.

The microscopic picture is that of a valvulitis as well as an endocarditis. Many new vessels have been formed in the thickened valve, and inflammatory cells are grouped in relation to these vessels. These are the same cells which constitute the Aschoff nodule, of which the most characteristic is the large multinucleated Aschoff cell, but the arrangement is more diffuse and less distinctive than it is in the myocardium. Leary has described a special type of endocardial lesion in the very early cases. This takes the form of a palisade of cells set at

right angles to the surface along the contact edge of the valve. Edema, a marked feature of the inflammatory lesion, accounts for much of the swelling of the valve. There is fibroblastic proliferation, followed later by the production of fibrous tissue. Meanwhile the endothelium covering the cusps degenerates, particularly along the line of closure, and is soon lost. Platelets are deposited on the raw surface together with a certain amount of fibrin, and it is these which form the vegetations. Fibroblasts and capillaries invade the vegetations, and these become converted into granulation tissue and organized, so that finally they blend with the thickened valve and become indistinguishable. The inflammation is not confined to the valves, for the endocardial lining of the left auricle may show the same type of lesion. In the acute stage there is roughening and in the chronic stage thickening of the surface lining. The chordæ tendinæ may contain Aschoff nodules, and the subsequent fibrosis causes shortening of these cords which is so marked a feature of mitral stenosis. In old lesions of the mitral valve the cusps show gross vascularity, the principal vessels being small thick-walled arteries or arterioles of musculo-elastic type (Koletsy). This vascularity may be regarded as one of the stigmata of rheumatic fever.

The consequences of all this are fatal to the health and efficiency of the valve. During the acute stage the inflamed edges of the cusps adhere together, and with the onset of fibrosis these adhesions become very firm, so that the cusps cannot open as they should, and there is narrowing or stenosis of the valves, both mitral and aortic. The new fibrous tissue makes the cusps rigid, and its contraction both in the cusps and in the chordæ tendinæ still further aggravates the stenosis so that the mitral opening may appear as a mere slit or button hole, or as a rigid funnel when viewed from the auricular aspect. Calcification of the injured cusps is common. It attains its most extreme form in the aortic valve of men over middle age in the lesion known as calcified nodular aortic stenosis.

**Myocardial Lesions.**—The typical myocardial lesion is the Aschoff nodule, which is fully described in Chapter VII. There is little to be seen in the gross appearance of the muscle in an acute case except a dilatation of the left ventricle, but tiny white specks may be seen under the endocardium of the left ventricle and left auricle. These are the Aschoff bodies. They are scattered through the fibrous tissue of the myocardium, most abundant at the base of the interventricular septum, numerous in the left auricle, not so common on the right side. They are submiliary in size, oval or lemon-shaped, and consist of a central necrotic, reticulated area, lymphocytes, plasma cells, and the characteristic large multinucleated Aschoff cells (Fig. 158). They are usually found in the adventitial coat of medium-sized arteries. The so-called Anitschkow myocyte is often found in large numbers in the cardiac lesions although not in rheumatic lesions elsewhere. It is a cardiac histiocyte which in inflammation shows increased cytoplasm, a highly characteristic serrated bar of chromatin in the center of the

nucleus, and fibrils radiating from the bar to the periphery. For a detailed account of the finer features of the Aschoff body the paper by Gross and Ehrlich should be consulted, in which will be found a description of the various stages of the life cycle through which the lesion passes. Fibroblasts are abundant and lay down collagen fibers, which replace the inflammatory lesion when the infection has died down. This may not happen for a long time, and Aschoff bodies have been found a number of years after the attack of rheumatic fever. As a result of the inflammation there is a varying degree of myocardial destruction, sometimes very great. The end-result is scarring. As the Aschoff lesion usually lies alongside a bloodvessel, so the rheumatic scar often is at the side of or surrounds a small artery. (Fig. 159.)

Aschoff nodules may not be found, for they are present in only about 80 per cent of cases. There may be a diffuse type of lesion instead of the circumscribed nodule. This is especially common in the



FIG. 158.—Large multinucleated Aschoff cells.  $\times 1100$ .



FIG. 159.—Healed Aschoff body.  $\times 50$ .

wall of the left auricle, and the damage it causes may be responsible for subsequent auricular fibrillation. Moreover the Aschoff nodule is merely the productive feature of rheumatic pathology. The exudative feature, though less marked in the myocardium than in the joints, is also important. The inflammatory edema, which is transient, no doubt interferes temporarily with the conduction bundle, and is responsible for the temporary functional disturbances which electrocardiographic studies show to be present in over 90 per cent of cases of rheumatic fever.

**Pericardial Lesions.**—Rheumatism is the commonest cause of acute pericarditis. The acute stage presents little that is characteristic of

rheumatism; it is merely an acute serofibrinous inflammation of a serous membrane. The fluid exudate is small in amount, only a few ounces, and is serous, never purulent. The chief element is the fibrin which is deposited on both surfaces of the pericardium giving it a shaggy or "bread-and-butter" appearance, as if two slices of buttered bread had been stuck together and then pulled apart. Even where no fibrin can be seen the natural gloss of the membrane is lost, but this may have to be looked for carefully.

In the *microscopic* picture any rheumatic lesions are apt to be hidden by the acute inflammatory reaction, but an occasional Aschoff body may be found in the subendothelial tissue. The surface endothelium is cast off, successive layers of fibrin are laid down, and this becomes organized by the invasion of new vessels and fibroblasts. The inflammatory cells are mostly lymphocytes and plasma cells with only an occasional polymorphonuclear leucocyte. The inflammation extends through the subpericardial fat down to the heart muscle.

The *after-effects* vary. There may be merely one or two opaque white patches of thickened epicardium known as *milk spots*. If absorption of the exudate is less complete there may be numerous adhesions. Finally there may be a completely *adherent pericardium*. Calcification of the lesions may occur, so that stony plates are formed on the surface of the heart.

**Aortic Lesions.**—The fibrous tissue of the aorta suffers in common with the fibrous tissue of the heart, so that Aschoff bodies or more diffuse lesions may be found in the adventitia. Although scars of the media have been described it is doubtful if these lesions ever weaken the wall sufficiently to produce an aneurism, thus differing from the similar but more extensive and destructive lesions of syphilis.

**Relation of Symptoms to Lesions.**—The *endocardial* symptoms or rather signs are the cardiac murmurs. The mitral systolic murmur is due to mitral regurgitation, which in turn is due to myocardial weakness and dilatation of the auriculo-ventricular ring. The mitral diastolic murmur, on the other hand, is valvular in origin, and is due to the stiffness of the cusps and the narrowing of the opening. The intensity of the murmur depends on the power of contraction of the auricle, and as this becomes weaker in the late stages, so the murmur may grow faint. Aortic incompetence with its diastolic murmur is due to retraction of the cusps and not to myocardial weakness, thus differing from mitral incompetence. Aortic stenosis due to rheumatism is uncommon. The *myocardial* effects may be acute or chronic. In the acute stage there may be death due to ventricular failure. In the chronic stage auricular fibrillation develops, owing to the degenerative lesion blocking the path of the impulse so that it goes round in a circle, and the pulse becomes totally irregular. The chief *pericardial* symptom is pain, just as the chief sign is a friction rub. Pain is often absent, though friction may be well marked. The friction rub is due to the rough surfaces rubbing together, but it is probable that some degree of tension and stretching is necessary before pain is produced, as is the case with pleural pain.

**Subacute Bacterial Endocarditis.**—Endocarditis due to demonstrable bacteria may be subacute or acute. The subacute form runs a course of from two months to one or two years, whereas the acute form is usually fatal in less than six weeks.



**Symptoms.**—The principal clinical features are continued fever, evidence of multiple embolism, endocarditis, a positive blood culture (streptococci), enlargement of the spleen, and clubbing of the fingers. As a cause of continued fever the disease should be classed with tuberculosis, typhoid fever, sepsis, and undulant fever. If a patient with a history of previous rheumatic fever or the physical signs of mitral stenosis or aortic stenosis or incompetence develops persistent evidence of toxemia such as malaise, weakness and fever, subacute bacterial endocarditis may be diagnosed even in the absence of embolic phenomena and a positive blood culture. The embolic phenomena are very varied: there may be crops of petechial hemorrhages in the skin, painful cutaneous nodules (Osler nodes), hemiplegia (cerebral vessels), sudden blindness in one eye (retinal artery), petechial hemorrhages in the retina, each with a white center (Roth's spots), pain in the splenic region, blood in the urine, diarrhea, and vomiting (mesenteric vessels). The blood shows a progressive anemia and usually a moderate leucocytosis, but often there is leucopenia with relative lymphocytosis. Toxic neutrophils are numerous, with basophilic cytoplasm, "toxic granules," and large vacuoles. Perhaps the most distinctive feature of the blood smear is the presence of peculiar large cells of endothelial or reticulo-endothelial type, resembling monocytes, with vacuolated or even foamy cytoplasm, coarse azure granules, and nuclei with sharp indentations and several nucleoli.

The *prognosis* in fully developed cases has hitherto been practically hopeless. The heart is beating muffled marches to the grave. The advent of penicillin therapy has greatly altered this outlook. When this agent is used sufficiently long and in sufficiently large doses the results are remarkably good. In many cases the blood rapidly becomes bacteria-free and the course of the disease is arrested. Much depends on the sensitivity of the strain of infesting streptococci to penicillin. Even when all the bacteria are finally killed, however, the patient may be left with badly damaged valves, and he may suffer from congestive heart failure and other cardiac complications.

**Etiology.**—As a rule the infection attacks previously damaged valves. An active or healed rheumatic lesion is present in from 75 per cent (Gross and Fried) to 90 per cent (Clawson) of cases. A congenital bicuspid aortic valve is a predisposing condition. Syphilis of the aortic valve is a rare antecedent. In a minority of cases the valves were previously healthy.

In about 95 per cent of cases the infecting organism is *Streptococcus viridans*, so that the condition is sometimes called streptococcus viridans endocarditis. The organism is of low virulence for animals; the fatal issue seems to be due to the failure of the immunological forces rather than to the virulence of the germ.

The probable *source of infection* is the mouth and throat. Transient bacteriemia, mostly with *S. viridans*, is common after tooth extraction and tonsillectomy, especially when the gums are infected (Okell and Elliott). Even biting on hard candies will cause an immediate blood infection in cases of pyorrhea. It is easy to understand how a valve damaged by rheumatism or by a congenital defect may be attacked by these circulating organisms.

**Lesions.**—The lesions may be divided into three groups: (1) cardiac, (2) embolic, and (3) general.

1. The *cardiac lesions* are mainly *valvular*; myocardial and pericardial lesions do not play an important part as they do in rheumatic disease of the heart. It seems probable that the infection is implanted on the

surface of the injured valve, rather than carried into its substance by newly formed vessels. The mitral valve is most often involved, the aortic valve coming next. Infection of the pulmonary valve is very rare.

The lesions are proliferative rather than destructive, but occasionally large portions of the cusps are destroyed as in the acute ulcerative form. The characteristic lesion takes the form of large friable, polypoid vegetations, very different from the tiny firm vegetations of rheumatic endocarditis. (Fig. 160.) They originate along the line of contact (proximal aspect of the cusp), but may cover the valve. At autopsy part of the valvular lesion may be calcified, showing that there have been attempts at healing. A highly characteristic feature is a tendency for the vegetations to spread on to the mural endocar-



FIG. 160.—Subacute bacterial endocarditis. The friable vegetations, the mural spread, and the old thickening of the aortic cusps are all very characteristic.

dium. This may be from the mitral valve to the wall of the left auricle or the chordæ tendinæ which may be weakened and rupture, or from the aortic valve to the wall of the ventricle. The distribution of the vegetations on the left auricle corresponds with that of the rheumatic lesion (MacCallum patch) in that region.

*Microscopically* the vegetations are amorphous masses consisting of fused platelets and fibrin. (Fig. 161.) A striking feature is the presence of masses of bacteria on the surface of the vegetations. They are best shown by Gram's stain, (Fig. 162.) but are quite evident in hematoxylin and eosin preparations. In some cases they are buried beneath a mass of platelets and fibrin; in such cases the blood culture will be negative. The valve itself is infiltrated by mononuclear cells, which are most numerous at the attachment of the vegetation to the



FIG. 161.—Subacute bacterial endocarditis. Large vegetation on thickened valve with masses of bacteria on the surface.  $\times 6.6$ .

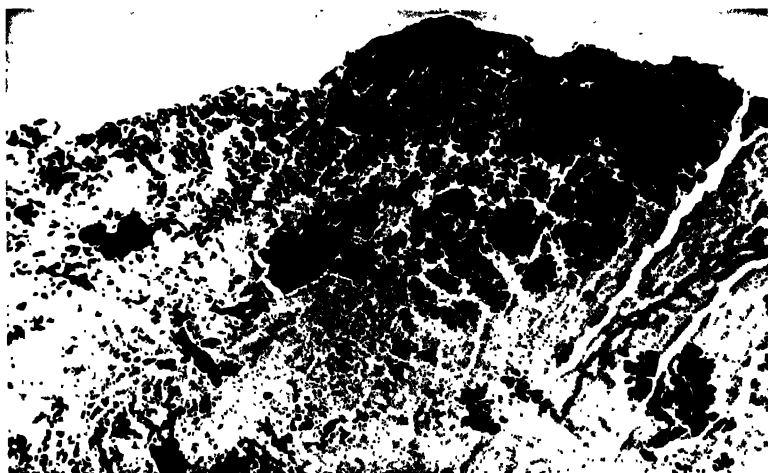


FIG. 162.—Subacute bacterial endocarditis. Bacteria stained black on surface of lesion. In this type of case the blood culture would probably be positive.  $\times 50$ .

cuspid. Larger multinucleated cells not unlike Aschoff cells may be present. There is a remarkable absence of polymorphonuclear leucocytes. No bacteria are found in the substance of the valve where the cells are, and there are no cells among the bacteria. That is the weakness of the situation from the immunological standpoint. Fibroblasts are present in the deeper parts of the lesion, and calcification is not uncommon. There is thus a distinct tendency to repair, and recovery might be possible if only the humoral defence could be strengthened.

Myocardial lesions are not numerous. There may be Bracht-Wächter lesions, little collections of polymorphonuclear leucocytes around necrotic material, practically tiny abscesses. In other cases Aschoff bodies may be present (see below). In the pericardium petechial hemorrhages are common; but pericarditis is rare.

2. Embolic lesions are very common, as the vegetations are friable and easily detached. They are non-suppurative, in contrast to the suppurative embolic lesions of acute ulcerative endocarditis. The petechial hemorrhages in the skin and the Osler nodes are usually regarded as embolic in origin, but there is no proof of this. It is more likely that they represent a perivascular reaction to the endotoxin, possibly allergic in nature. Large infarcts due to blocking of medium-sized vessels are seen in the enlarged spleen and in the kidneys. Many of the more minute lesions appear to be due to toxic necrosis of vessel walls rather than to emboli, although the name embolic is still retained. This is particularly true of the so-called focal embolic glomerulonephritis originally described by Löhlein and known as the Löhlein lesion. Only a few glomeruli are involved and usually only a part of a glomerulus. A few loops of the tuft are blocked with an accompanying acute reaction, as a result of which red blood cells appear in the capsular space and pass out into the urine. Although these lesions are commonly believed to be embolic it appears more probable that the blocking of the loops is due to a toxic focal proliferation associated with capillary thrombosis and necrosis. Healing occurs owing to the ready access of cells to the irritant, and a homogeneous mass of organized tissue is formed in one segment of the tuft, giving an appearance which is pathognomonic of this disease. In the acute stage small red spots are seen on the surface when the capsule is stripped off, an appearance known as the "flea-bitten kidney." Occasionally there is a diffuse glomerulonephritis with renal insufficiency terminating in uremia. In the central nervous system there may be cerebral embolism and softening in the internal capsule with a resulting hemiplegia, or tiny inflammatory lesions may be scattered through the brain. The retina may show pathognomonic transient "canoe-shaped" elliptical hemorrhagic spots with a pale center. Mycotic aneurisms may be produced in the cerebral, superior mesenteric, and other arteries.

3. The general lesions are of less importance. Some are due to cardiac failure, some to toxemia. Among the latter are cloudy swelling and fatty degeneration of the liver and kidneys, enlargement of

the spleen, a secondary anemia, and in rare cases degenerative lesions of the spinal cord like those of subacute combined degeneration.

**Relation of Symptoms to Lesions.**—The *cardiac signs* (murmurs) are due to the vegetations and the valvular destruction. But at first there may be no murmurs, and of course murmurs are no proof of an active endocarditis. Later in the disease the valvular insufficiency leads to cardiac decompensation and enlargement of the heart. Cardiac pain is not uncommon. I know no explanation of this. Death is usually due to cardiac failure, cerebral embolism, uremia, or some intercurrent infection.

The *embolic phenomena* are readily explained by the friable nature of the large soft vegetations. The blood in the urine which is so characteristic a feature is due to the embolic glomerular lesions. It is better to speak of red blood cells rather than blood, for the microscope is generally needed for their detection, and as they are not present every day the examination may have to be repeated a number of times. The occasional occurrence of renal insufficiency and uremia is due to a rather uncommon diffuse glomerulonephritis.

**Rheumatic and Subacute Bacterial Endocarditis Compared.**—The view is gradually gaining ground that these apparently distinct diseases are really manifestations of the same fundamental process. One is certainly streptococcal in origin and the other probably is. The subacute form is usually preceded by the rheumatic. *Streptococcus viridans* may be found in the blood in rheumatic endocarditis although with considerable difficulty. Clawson and Bell have shown that the transition from one to the other may be so gradual that we cannot tell where the one ends and the other begins. The rheumatic type of vegetation can often be seen on the same valve as the vegetation of the subacute type. The microscopic picture of both is a proliferative valvulitis, but in the subacute form a large infected thrombus is added to the lesion, and this thrombus is responsible for the characteristic embolic phenomena. In some of my own subacute cases I have been impressed with the very close resemblance of the microscopic picture to that of rheumatic endocarditis. Clawson and Bell found Aschoff nodules in 11 per cent of cases of subacute endocarditis as compared with 87 per cent in rheumatic hearts. One difficulty is that rheumatic fever is believed to be due usually to hemolytic streptococci, whereas subacute bacterial endocarditis is caused by *Streptococcus viridans*. It is quite possible that the rheumatic infection, by rendering the valves vascular, may merely pave the way for subsequent infection with *Streptococcus viridans*, just as a congenital lesion of the aortic valve predisposes to an attack of subacute bacterial endocarditis. Such a view would be consistent with the presence of both types of lesion in the same heart.

The matter cannot be settled finally from observations on human cases. Clawson injected both *Streptococcus viridans* and *Streptococcus hæmolyticus* into the ventricular cavity of rats several times at weekly intervals. He succeeded in producing an endocarditis both rheumatic-like and bacterial in type. The former bore a marked resemblance, both gross and microscopic, to the verrucose vegetations of acute rheumatic fever. No bacteria were found in the rheumatic-like lesions, whereas

they were abundant in the bacterial type of lesions. It would appear as if the pure platelet thrombus becomes infected to produce the bacterial type of vegetation. These experimental observations support the view that acute rheumatic endocarditis and bacterial endocarditis are etiologically similar although differing in their tissue response to the infecting agent.

**Acute Bacterial Endocarditis.**—This is a group, a good deal less common than the preceding form, in which an acute destructive process is caused by pyogenic cocci which produce suppurative lesions not only in the valves but also in the organs where emboli lodge. The course of the disease is six weeks or less, so that this form is also called malignant endocarditis. The chief bacteria responsible are *Streptococcus hæmolyticus*, *Staphylococcus aureus*, pneumococcus, and occasionally gonococcus. The primary focus of infection is usually obvious, being some suppurative lesion of the skin (boil, carbuncle), bones (osteomyelitis), uterus (puerperal sepsis), lung, or prostate. The endocarditis is often merely a complication in an already serious disease such as osteomyelitis or puerperal sepsis.

The two chief features of the valvular lesions are the very large, exuberant, friable vegetations and the marked destruction, so that a cusp may be perforated or largely ulcerated away and the chordæ tendinæ destroyed. The mitral and aortic valves are affected with equal frequency, and the tricuspid often suffers. Involvement of the right side alone suggests gonococcal infection. In most cases it is impossible to distinguish between the acute and subacute forms from the gross appearance. The *microscopic* picture is one of acute sup-puration, the cusp being crowded with polymorphonuclear leucocytes. The vegetation has the same microscopic appearance as in the subacute form.

*Embolic abscesses* are formed in all parts of the body, especially the skin, myocardium, brain, and kidneys. Both kidneys are riddled with abscesses, a condition known as the pyemic kidney. The general clinical and pathological picture at the time of death is one of acute pyemia.

**Atypical Verrucous Endocarditis.**—In 1924 Libman and Sacks described a form of endocarditis characterized by flat vegetations spreading on to the mural endocardium which may be present on all the valves, most often the tricuspid, and in the valve pockets. Neither Aschoff lesions nor streptococci could be demonstrated. It now appears that the endocarditis is merely one manifestation of a generalized disease, which has been called *Libman-Sacks disease*, in which the principal features are disseminated lupus erythematosus, arthritis, polyserositis, myositis, diffuse vascular-glomerular disease of the kidneys, and enlargement of lymph nodes. Only one or two of these lesions may be present. There may be no macroscopic endocarditis. The disease, which occurs in young people and runs a subacute course with fever and a progressive anemia, resembles rheumatic fever in its widespread distribution, and differs sharply from bacterial endocarditis which is essentially a cardiac condition. The etiology is unknown.

**Terminal Endocarditis.**—In many chronic diseases (nephritis, diabetes, cancer) small vegetations of the rheumatic type may be found on the valves

at autopsy. They seldom show the bead-like arrangement of rheumatic vegetations. They have been classed as intermediate or thrombotic forms. Allen and Sirota believe that the condition is degenerative rather than thrombotic, and suggest the name *degenerative verrucal endocarditis*. They point out that the lesions are hillocks of degenerated, swollen, valvular collagen. The verrucæ may be single or multiple. They are not necessarily terminal, for they may heal to form fibrous nodules or a bulbous swelling of the free edge. The cause is unknown, possibly toxic or due to stress and strain.

**Syphilitic Endocarditis.**—Syphilis attacks only the aortic valve, never the mitral. As it forms a complication and extension of syphilitic aortitis, never occurring apart from aortitis, it will be considered in connection with that condition.

**Tuberculous Endocarditis.**—This is an extremely rare form of endocarditis. The vegetations are small and of the nature of granulations. No tubercles can be found in the valve, but tubercle bacilli are present in the vegetations.



FIG. 163.—Mitral stenosis. Small left ventricle, narrowing of mitral opening, great dilation of left auricle and right side of heart.

### THE VARIOUS FORMS OF VALVULAR LESIONS

**Mitral Stenosis.**—Most, if not all, cases of mitral stenosis are rheumatic in origin. It is possible that mild forms of subacute bacterial endocarditis may end in healing with adhesion of the cusps. It is much commoner in women than in men. The left auricle and the right side of the heart are greatly dilated owing to the obstruction, but the left ventricle is normal in size or even smaller than normal.

(Fig. 163.) When the heart is opened the left auricle is seen to be enormous. It may contain as much as 500 cc. instead of the ordinary 30 or 40 cc. The valve looks like a deep funnel, the walls of which are formed by the fused cusps. The blood rushing through this rigid funnel causes a vibration of its walls which is responsible for the diastolic murmur and thrill with or without presystolic accentuation. The opening may be a mere button-hole which will hardly admit the tip of the little finger. (Fig. 164.) The thickened and sclerosed cusps

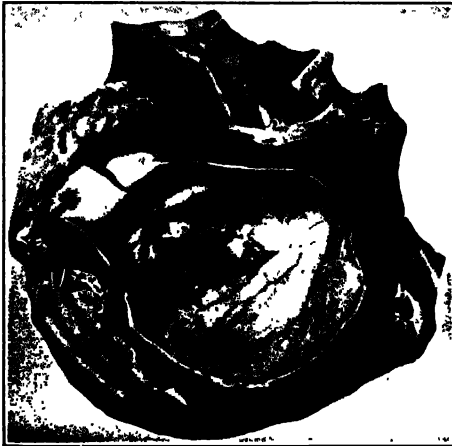


FIG. 164.—Mitral stenosis. The thickened valves have fused so as to cause extreme narrowing of the opening.

may become calcified, so that the valve can neither open nor shut, a combined condition of stenosis and incompetence. The chordæ tendinæ may be so thickened and shortened that the papillary muscles seem to be implanted on the valve. There may be thrombus formation in the dilated left auricle, particularly in the auricular appendix. This is very important, because the clot may become detached and give rise to cerebral embolism. Moreover a thrombus often forms in the right auricle, and this may cause pulmonary embolism, especially when

auricular fibrillation sets in. Thus, though in rheumatic endocarditis there are no friable vegetations which can become detached, yet embolism is a common complication of mitral stenosis. In rare cases a ball thrombus may be present, a large globular mass lying free in the auricle.

The *general effects* of mitral stenosis are those of chronic venous congestion. (See Chapter III.) This is most marked in the lungs and liver. The distended pulmonary capillaries may rupture into the alveoli causing hemoptysis. Mitral stenosis is the commonest cause of hemoptysis or the coughing up of blood. The common explanation for this is the distended condition of the pulmonary capillaries, but it seems more probable from the observations of Ferguson and his associates that the hemorrhage takes place from varicosities in the submucous bronchial veins. These workers by means of injection methods showed that there is a free communication between the main pulmonary veins and the bronchial veins, and that in mitral stenosis the latter veins become dilated and varicose. Areas of hemorrhage and infarction are common in the lungs, and there are great numbers of heart failure cells in the alveoli. Owing to extravasation of blood there is fibrosis of the septa, and the lung becomes brown and firm, a condition known as



*brown induration.* The pulmonary artery and its branches often show marked atheroma owing to the continued strain though the aorta may be normal. The pulmonary arterioles may show a hyperplastic sclerosis and necrosis similar to that seen in the renal arterioles in malignant hypertension. Parker and Weiss point out that in severe cases of mitral stenosis there may be great thickening of the basement membrane supporting both the alveolar epithelium and the vascular endothelium, and that the space between them may become widened by edema, so that the alveolar tissue may be twenty times thicker than normal. As a result there is a grave interference with gaseous exchange, the blood being separated from the alveolar air by so thick a partition. This explains why it is that intense cyanosis may persist in spite of myocardial improvement. The liver shows marked congestion and may become indurated. The other organs are congested to a lesser degree.

**Mitral Incompetence.**—The organic as opposed to the functional form of mitral incompetence is due either to sclerosis and contraction of the cusps or to dilatation of the ring. The common cause is rheumatic endocarditis. Subacute bacterial endocarditis will also cause incompetence because of the large vegetations, the sclerosis, and the occasional destruction of the cusps. In old age the cusps may undergo degeneration and calcification which will interfere with their efficiency. The condition of the heart is similar to that of mitral stenosis except that the left ventricle is also much dilated owing to the increased amount of blood which it has to accommodate. In the end-stages the heart is greatly enlarged.

**Aortic Incompetence.**—The two principal causes of aortic incompetence are rheumatic endocarditis and syphilitic aortitis. Two additional causes are subacute bacterial endocarditis and the nodular sclerosis of old age. Incompetence due to endocarditis is caused by adhesions, thickening, and contraction of the cusps. It may be combined with stenosis, and is seldom so extreme as the incompetence caused by syphilis. In the syphilitic form the incompetence may be due to one or more of three factors: (1) dilatation of the aortic ring caused by destruction of the elastic tissue; (2) widening of the commissures; and (3) retraction of the cusps and thickening of their free edge. The dilatation may be so great that the valve becomes useless though the cusps may be healthy, and the incompetence is complete. High blood-pressure and severe physical strain naturally aggravate the condition. It is doubtful if atheromatous degeneration alone can cause incompetence, but the possibility cannot be denied.

The condition of the heart is the opposite of that of mitral stenosis. Here the heart is all left ventricle. The heart is extremely enlarged and globular in outline, the *cor bovinum*. The left ventricle is greatly hypertrophied as well as dilated. The condition of the aortic valve will depend entirely on whether the incompetence is endocardial or syphilitic in origin.

The *clinical picture* is highly characteristic, but is much more extreme

in the syphilitic than in the endocardial form. The symptoms and signs are due to the escape of blood from the aorta back through the incompetent valve. The arteries thus contain too much blood during systole and too little during diastole. This accounts for the leaping peripheral vessels ("the dance of the arteries"), the capillary pulsation, the water-hammer pulse (Corrigan pulse), the low diastolic pressure, and the high pulse-pressure, the giddiness and attacks of syncope due to cerebral anemia. The diastolic murmur which is the most characteristic physical sign is due to the blood escaping back into the ventricle.

**Aortic Stenosis.**—This is quite uncommon in a pure form, although in the rheumatic variety of aortic incompetence the rigid and adherent cusps may be unable to open fully so that a relative degree of stenosis is produced. Pure aortic stenosis usually occurs in men over fifty years of age, and is of the *calcified nodular type*, best called *calcific aortic stenosis*. The cusps adhere together to form a kind of diaphragm as in mitral stenosis, but the most striking feature is the presence of warty calcified masses which may cover the cusps or be confined to the base. The entire valve is incredibly hard and rigid. The calcification can be seen in roentgen-ray films. There is marked difference of opinion as to whether the lesion is rheumatic in origin or degenerative (arteriosclerotic) in character, the so-called Mönckeberg type. The fact that the condition is a clinical entity does not necessarily mean that it is an etiological entity, so that some cases may be rheumatic and others degenerative. Hall and Ichioka consider that all cases are rheumatic in origin, although the rheumatic lesions in the myocardium may be largely healed and hard to recognize. In their series of cases 60 per cent had solitary aortic lesions, while 40 per cent had healed mitral lesions. Karsner also believes that calcific sclerosis is essentially rheumatic in origin. It must be remembered that the stigmata of previous rheumatic disease can frequently be detected in any series of hearts which are examined with sufficient thoroughness, so that their presence in a case of calcific aortic stenosis is no proof that the latter lesion is rheumatic in origin. It seems probable that many cases should still be regarded as degenerative in nature, especially when the mitral valve is entirely normal.

The heart shows a perfect example of pure or concentric hypertrophy of the left ventricle, although toward the end it may undergo dilatation. The average weight is about 650 grams, and in one of Christian's cases it weighed over 1000 grams. The aorta is remarkably smooth and free from atherosclerosis for patients over middle age, and it almost seems as if the vessel wall has been protected by the stenosis. As so little blood enters the aorta the pulse is small and fainting attacks are common. The pulse tracing with its slanting upstroke and rounded camel's hump speaks eloquently of the resistance at the aortic opening. The most characteristic physical sign is a rough rasping systolic murmur and thrill at the aortic area. If incompetence is also present, a diastolic murmur will be added.

**Tricuspid Stenosis.**—Rheumatic infection may spread from the mitral to the tricuspid valve ring, and the subsequent endocarditis may cause the leaflets to be glued together, with resulting stenosis.

**Pulmonary Stenosis.**—In most instances this lesion is congenital (developmental) in origin. The rare acquired cases are due to rheumatism.

### CHRONIC HEART FAILURE

The most common cause of death is failure of the heart. This may be slow or sudden. The three great causes of gradual failure are valvular disease, arteriosclerotic narrowing of the coronary arteries and arterial hypertension. We may therefore speak of valvular heart disease, arteriosclerotic heart disease, and hypertensive heart disease. Hypertensive heart disease is commoner than all the other forms put together.

In a pure obstructive lesion such as aortic stenosis the chamber proximal to the obstruction will undergo a work *hypertrophy*, the muscle fibers becoming larger but not more numerous. MacMahon, however, has shown that in idiopathic cardiac hypertrophy of infants true proliferation of the fibers may occur, and in rare instances the same is true of children after severe toxic injury to the heart. The best example is seen in the so-called *concentric hypertrophy* of the left ventricle in arterial hypertension, whether of the primary "essential" type or secondary to chronic nephritis. In arteriosclerotic heart disease there may or may not be hypertrophy, depending on whether there is or is not an associated hypertension.

In course of time *dilatation* is added to hypertrophy. This may be compensatory or may be due to failure. Compensatory dilatation is seen in aortic incompetence. During diastole the blood regurgitates from the aorta through the incompetent valve into the ventricle in addition to that entering it from the auricle. If venous congestion is to be avoided the ventricle must dilate. At the same time it hypertrophies in order to cope with the increased amount of blood it has to expel with each contraction.

Dilatation from failure is likely to be the end of every cardiac lesion if the patient lives long enough. For a time hypertrophy can look after the increased load, but there comes a time when the effort fails, the muscle becomes exhausted, and the cavity dilates. This is more apt to occur when the myocardium itself is not healthy, as from fatty degeneration or myocardial scarring. A healthy heart may be acutely dilated as the result of very great and sudden exertion. The cavities will gradually return to normal size with rest in bed, but there may be functional cardiac disability for some time.

Cardiac failure may be mainly left ventricular, or mainly right ventricular, or both. In chronic left ventricular failure the symptoms and signs are those of pulmonary hypertension with normal pressure in the systemic veins, i. e., cardiac dyspnea and accentuated pulmonary second sound. Right ventricular failure follows upon prolonged pulmonary hypertension, which in turn may be due to left ventricular

failure, to mitral stenosis, or to intrinsic pulmonary conditions. The term *cor pulmonale* is applied to a condition of enlarged right heart (first hypertrophy and later dilatation) and dilated pulmonary artery due to narrowing of pulmonary arterioles and the capillary bed by pulmonary fibrosis, emphysema, or (rarely) pulmonary endarteritis obliterans; silicosis is an important cause of vascular obstruction; chest deformities (spinal curvature, etc.) may cause mechanical obstruction. The final stage of cardiac failure is *congestive heart failure*, with engorged systemic veins, a large and tender liver, swollen legs, ascites, pleural effusion especially on the right side, and marked cyanosis.

In infectious diseases heart failure is a frequent cause of death, and at autopsy the heart is often found to be remarkably soft and flabby. This may be due in part to the action of toxins on the myocardium, but a major factor appears to be peripheral circulatory failure. The strength of the cardiac contraction depends on the load placed on the muscle, and for a normal load there must be adequate filling of the ventricles during diastole and adequate venous flow from the periphery. If the blood collects in the dilated capillary plexuses in the viscera and skin in severe infections, shock, etc., or in the pulmonary vessels in influenza, the heart is not given enough work to do, loses its tone, and finally fails.

### LESIONS OF THE MYOCARDIUM

**Acute Bacterial Myocarditis.**—Two forms of acute inflammation of the myocardium are recognized, bacterial and toxic. These are commonly known as interstitial and parenchymatous, but it is time that these meaningless terms were given up. The toxic form, indeed, is not even an inflammation. In both forms the heart is very soft and flabby, so that it flattens out on the autopsy table. It has a pale dead color, and the cavities are dilated. The best example of acute bacterial myocarditis is the suppurative form, but the rheumatic, syphilitic, and tuberculous varieties all come under this heading.

**Suppurative Myocarditis.**—This is usually a manifestation of pyemia, but the infection may spread from an acute ulcerative endocarditis or an acute pericarditis. Miliary abscesses are scattered through the fibrous tissue of the heart, or there may be a diffuse infiltration with polymorphonuclear leucocytes. There is marked destruction of the muscle fibers, and the condition ends in death.

**Rheumatic Myocarditis.**—This has already been described. The rheumatic lesion or Aschoff body is a focal collection of inflammatory cells in the interstitial tissue, but the lesions may be diffuse instead of focal. If the myocarditis is very acute it may kill the patient. Recovery is the rule, and small scars remain to mark the site of the lesions.

**Syphilitic Myocarditis.**—This is described in connection with Syphilis of the Heart.

**Tuberculous Myocarditis.**—This is very rare. There may be miliary tubercles scattered through the myocardium. Still more rarely there are large yellow caseous lesions of the myocardium unlike anything else found in the heart.

**Subacute Myocarditis of Unknown Etiology.**—There is a small group of obscure cases characterized by rapid myocardial failure or sudden death in which granulomatous or subacute inflammatory lesions are found in the myocardium. It is probable that they represent a heterogeneous collection and not a definite entity, so that no really satisfactory name has been suggested.

It is reported in the literature under such names as idiopathic myocarditis, Fiedler's myocarditis (first reported by Fiedler in 1899), and isolated myocarditis. A good review of the subject is given by Magner, who reports a case from my laboratory. The patient had previously been in good health, and died unexpectedly after the removal of a non-toxic goiter; scattered through the myocardium were foci of mononuclears and giant cells.

**Acute Toxic Myocarditis.**—This is a degenerative condition rather than an inflammatory one. *Diphtheria* offers a typical example. There is an acute degeneration of the muscle followed later by a secondary inflammatory reaction. The muscle fibers are swollen and granular and have lost their striations. The essential change is a hyaline degeneration and necrosis. For some reason only parts of the fiber may be affected. Fatty degeneration is not an important factor as a cause of myocardial weakness, although often blamed. After some weeks there is evidence of degeneration of muscle, the nuclei and the living fibers bordering the dead area undergoing longitudinal splitting. The interstitial tissue in relation to the necrotic muscle shows an inflammatory reaction with polymorphonuclears, lymphocytes, and later fibroblasts. This reaction may be looked upon as phagocytic and reparative in nature.

The *sulphonamide drugs* may cause an acute interstitial myocarditis both in man and in experimental animals (French and Weller). The exudate is rich in eosinophils. In these days of universal chemotherapy this observation is of importance to the pathologist.

**Chronic Myocarditis: Myocardial Fibrosis.**—The term chronic myocarditis is in common use, but it indicates little or nothing. Myocardial fibrosis, on the other hand, indicates what is found in the heart, a condition of scarring with little or no sign of inflammation. The fibrosed heart is firm and rigid, not soft and flabby as in acute myocarditis. White strands may be seen on the cut surface, especially in the anterior wall of the left ventricle near the apex and in the interventricular septum, or they may only be visible in microscopic sections.

It is evident that what is called chronic interstitial myocarditis resolves itself largely into a question of *myocardial scars*. The problem is to determine the antecedent factor responsible for the scars. There are two main possibilities: (1) coronary artery occlusion, and (2) old inflammatory and necrotic foci (rheumatism, diphtheria, typhoid fever). As we are dealing with an end-product it is often impossible to say which of these two was at fault. Undoubtedly the commonest cause of myocardial scars is coronary artery occlusion, either gradual or sudden.

**Heart-block.**—The conduction system of the heart may be interrupted by a scar. Normally the impulse starts at the sino-auricular node (the pacemaker), and passes by way of the auriculo-ventricular node of Tawara and the bundle of His to the right and left ventricles. An interruption of this path will leave the auricles beating at a normal rate, but the ventricles drop to a much slower rate of their own, about one-half that of the auricles, so that the pulse is correspondingly slow (bradycardia). The difference between the rate of the jugular pulse (auricular) and radial pulse (ventricular) is a

measure of the degree of heart-block. The chief effect of the slowing of the heart beat is felt by the brain. There may only be dizziness due to the cerebral anemia, but in the more severe cases there may be attacks of fainting (syncope). Finally there is the complete picture of the *Stokes-Adams syndrome* with convulsions added to the syncope often ending in death.

There are two principal forms of heart-block: (1) auriculo-ventricular block due to a lesion in the upper part of the bundle, and (2) bundle-branch block due to a lesion in one of the two main ventricular branches. These forms may readily be distinguished in the electrocardiogram, which shows what is going on in the different parts of the heart during the various stages of the cardiac cycle. In bundle-branch block there is right or left ventricular predominance, depending on which branch of the conduction bundle is affected.

**Lesion.**—The lesion in heart-block is anything which interrupts the continuity of the conduction bundle. This may be an acute process or a scar. The two most important causes are coronary artery occlusion and syphilis. The occlusion may be sudden with the production of an infarct, or slow with ischemic necrosis and scarring as a result. The syphilitic lesion may be an active one or a scar. An interventricular septal defect may cause congenital heart-block. Rheumatism, diphtheria, and typhoid fever may give rise to lesions in the course of the bundle. Extension of a process of degeneration and calcification of the aortic valve into the adjoining region which contains the bundle may cause complete heart-block. As the lesion which causes heart-block may be quite minute, it is necessary to cut serial sections of the entire length of the bundle, a rather formidable undertaking.

**Syphilis of the Heart.**—For practical purposes cardiac syphilis is syphilitic aortitis (page 391). Myocardial scars and focal collections of lymphocytes and plasma cells have been attributed to syphilis, but without justification. *Gumma* of the myocardium is a rare condition. It is usually situated in the upper part of the interventricular septum, where it may interrupt the conduction bundle and cause heart-block.

**Hypertensive Heart Disease.**—The four principal forms of heart disease are those due to rheumatic fever, bacterial endocarditis, coronary artery occlusion, and arterial hypertension. The last of these is the commonest. A person with hypertension may live for many years without showing any symptoms. During this time the heart is accommodating itself to the increased work it has to do. As the patient gets older, as the coronary arteries become narrowed, and particularly if the blood-pressure continues to rise, the day will come when the myocardium is no longer equal to the strain, and congestive heart failure develops.

The most striking feature is marked hypertrophy of the left ventricle, so that when the heart is grasped it feels like a closed fist. The walls are rigid, the heart maintaining its curved form when laid on the table. In the late stages dilatation may be added to the hypertrophy. Strands or patches of fibrous tissue are often scattered through the wall of the left ventricle.

Apart from this fibrosis, which may be minimal in degree, the heart muscle appears normal. The individual fibers show no sign of degeneration, and are frequently hypertrophied. Why they should fail remains a mystery. What seems to be powerful muscle is unable to expel the blood from the heart with any vigor. It is evident that in the myocardium morphological appearance does not necessarily correspond with functional capacity.

**CORONARY ARTERY OCCLUSION**

Three things may happen when one of the larger branches of the coronary arteries is occluded: (1) The patient may die immediately. By far the commonest cause of sudden death is cardiac failure; indeed it is the only thing which will kill a person *instantaneously*. The commonest cause of sudden cardiac failure is coronary occlusion. (2) He may linger for a few hours or days. (3) In many cases he recovers, at least for a time. Death from coronary occlusion is common among doctors and other professional men.

As regards *pathogenesis*, the occlusion may be produced in four ways: (1) atheromatous narrowing of the vessel; (2) thrombosis in an already atheromatous artery; (3) syphilitic aortitis of the root of the aorta sealing the mouths of the coronaries; (4) in rare cases an embolus from a vegetation of the valve may block a vessel. When an embolus blocks a main coronary artery, death occurs with dramatic suddenness. Occasionally syphilitic arteritis of the coronary artery may cause occlusion. At the site of the atheromatous plaque numerous lymphocytes are sometimes present in the adventitia. This appearance must not be mistaken for the perivascular cellular infiltration characteristic of syphilis. Of these various causes by far the most important is arteriosclerosis, with or without an added thrombosis. For this reason the general cardiac condition from which the patient suffers may be called *arteriosclerotic heart disease*. The coronary arteries share in the general atherosclerosis of old age. In young adults, however, the coronaries may be the only vessels affected, the condition being much more common in men than in women. Dock points out that the intima of the coronaries lying in the epicardium is much thicker than that of any artery of similar caliber elsewhere in the body, and that this is much more pronounced in the male, being present even in infants. This anatomical peculiarity may have some etiological significance.

Duguid suggests that some (he says many) of the lesions regarded as atheromatous are arterial thrombi which have been transformed into fibrous thickenings by the process of organization. Most of the thrombi consist of fibrin, and these are converted into fibrous patches which fuse with the intima and become covered by endothelium. When the thrombus contains large numbers of red blood cells, fatty degeneration occurs, and this may give a picture indistinguishable from that of an atheromatous plaque.

The importance of hemorrhage into an atheromatous plaque in the intima was first pointed out by Paterson and later by Winternitz. The hemorrhage is due to rupture of capillaries caused by atheromatous softening. In the majority of cases of coronary thrombosis intimal hemorrhage can be demonstrated, but numerous blocks and serial sections may be needed for this demonstration. Even without thrombosis the hemorrhage may produce great narrowing of the lumen by causing bulging of the intima. When hemorrhage is marked it can be recognized with the naked eye in cross-section of the artery. Intimal

hemorrhage offers an explanation of those attacks of coronary occlusion which are precipitated by sudden exertion or excitement, both of which cause a temporary rise in the blood-pressure. In more than one-half of the cases of acute occlusion the heart is enlarged (overweight), due possibly to hypertension, which may be an etiological factor. Some workers, however, believe that coronary arteriosclerosis may lead to cardiac hypertrophy quite independent of hypertension. In many cases of coronary thrombosis there is neither hypertrophy nor any evidence of hypertension.

The *relation of trauma* to coronary thrombosis is difficult to decide. Many cases are reported in the literature where a non-penetrating injury to the precordia has been followed almost immediately by symptoms of thrombosis and infarction. In such cases it is reasonable to assume that trauma precipitated the thrombosis. The coronary artery is already the site of atheroma, and trauma may cause hemorrhage into an atheromatous plaque, thus initiating thrombosis.

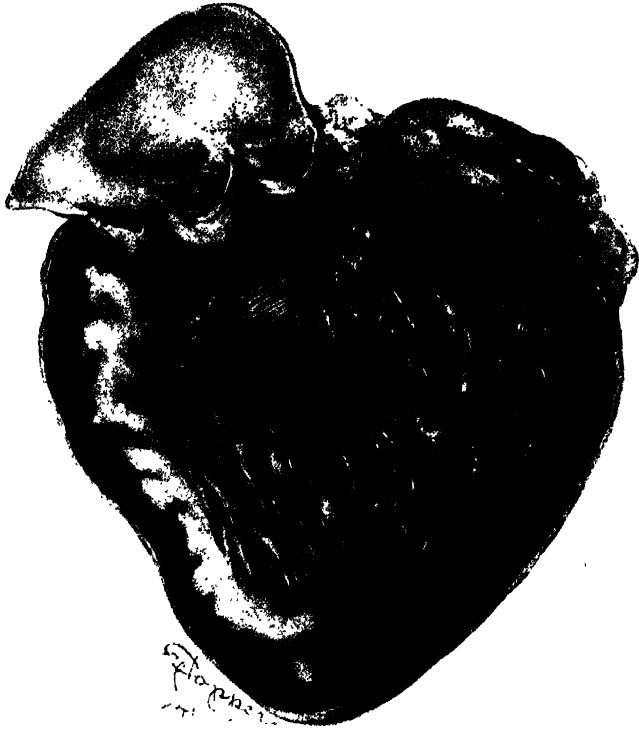
**Symptoms.**—Parkinson remarks that when a man of advancing years is seized while at rest with severe pain across the sternum, which continues for hours and which is accompanied by shock, you may diagnose coronary occlusion. The chief incidence is between forty-five and sixty years of age. After sixty years the disease is not so common because of increasing anastomoses and vascularity in the myocardium of the left ventricle. Sudden death from extreme atheromatous occlusion of the coronary arteries may occur in the early twenties and thirties, as illustrated by the report of French and Dock on 80 cases in soldiers between the ages of twenty and thirty-six. The pain is abrupt in onset; he is well one minute and in agony the next. It is usually precordial but may be epigastric, and as there is often slight fever and a moderate leucocytosis, an acute abdominal condition is apt to be diagnosed. Newspaper accounts of death from acute indigestion are examples of coronary occlusion. Sometimes there is no pain. Dyspnea is the most constant symptom. The face is ashy pale and bathed in sweat. Shock is present, but is not to be explained by any of the current theories for traumatic shock. It is a manifestation of heart failure. There may be *angor animi*, a feeling of impending dissolution. Weak heart sounds, acute pulmonary edema, enlargement of the liver, and albuminuria are common features. There is an increase in the sedimentation rate, usually about the fourth or fifth day. A pericardial friction rub which is characteristically fleeting is often present. The *prognosis* varies. About one-half die suddenly. Of the remainder about one-half make a complete functional recovery and are able to resume work. The other half develop congestive heart failure or anginal attacks.

The occlusion is usually in the anterior descending branch of the left coronary about 2 cm. from the commencement. Distal to the occlusion there may or may not be a thrombus. The atheromatous patch may block the lumen so completely that not even the finest probe can be passed along it. The result of acute occlusion, most readily understood when thrombosis completes the occlusion, is the production of a myocardial infarct. Of course, if the occlusion causes sudden death there will be no time for an infarct to be produced.

The area involved includes the anterior part of the interventricular septum, the apex, and the anterior part of the wall of the left ventricle. When the right coronary is occluded the infarct includes the posterior



## PLATE VIII



Recent Infarct of Heart

The yellow necrotic tissue in wall of left ventricle is edged by a narrow dark red border



half of the interventricular septum and the posterior part of the wall of the left ventricle, with little or no involvement of the right ventricle. The contrast between the two forms is marked, but has only recently been recognized. If death has been instantaneous there will, of course, be no infarct. The areas are irregular in shape, yellow in color, and often surrounded by a red zone. (Plate VIII.) The larger areas may undergo softening (*myomalacia cordis*), and this may lead to rupture of the heart. If the endocardial surface is involved a thrombus will be formed on the necrotic area, and if the pericardial surface is involved there will be a patch of pericarditis. The area of pericarditis is more extensive than the apparent area of infarction. Embolism, sometimes fatal, may occur as a result of the mural thrombus becoming detached. Gradually the infarct becomes replaced by fibrous tissue, so that it is represented by a white patch of scar visible both on the endocardial and on the cut surface, with corresponding thinning of the wall of the

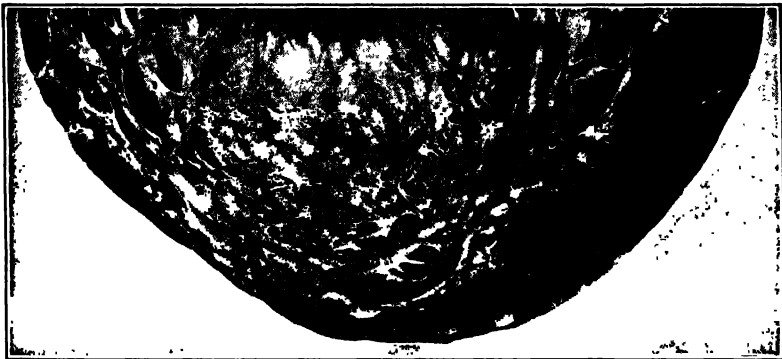


FIG. 165.—Myocardial fibrosis following infarct. The wall of the ventricle at one side and at the apex is markedly thinned.

ventricle. (Fig. 165.) Should the patient survive for some time the weakened area will give way and bulge outward, so that an *aneurism of the heart* is formed with marked thinning of the wall. (Fig. 166). This usually involves the anterior wall of the left ventricle near the apex. In course of time this aneurism may rupture, causing sudden death. Sometimes a thrombus will form on an area of scarring, even though there is no recent necrosis. A heart which is the site of an old infarct is usually hypertrophied; in many cases this hypertrophy is not related to hypertension.

The *microscopic appearance* of the infarct depends on its age. The sequence of events was determined in the experimental animal by Karsner and Dwyer in 1916, and more recently in the human subject by Kenneth Mallory and his associates. Necrosis is not evident till the end of six hours, when the muscle fibers become hyaline and stain a deeper red with acid dyes. The striations are indistinct and finally lost, the clear outline of the fibers are now smudged, the spaces between

the fibers are filled with granular debris, and the nuclei disappear. Some of the fibers may become swollen and vacuolated before disintegrating. (Fig. 167.) In the *first week* there is slight polymorphonuclear infiltration of the necrosed area at the end of twenty-four hours, and by the fourth day this has become marked. Removal of the necrosed tissue begins. In the *second week* this removal is carried out by great numbers of pigment-filled macrophages, which replace the polymorphonuclears. The pigment is partly muscle pigment and partly blood pigment resulting from hemorrhage from greatly distended vessels. New capillaries and fibroblasts grow into the infarcted area. In the *third week* removal



FIG. 166.—Aneurism of heart showing bulging and thinning of ventricular wall.

of the dead muscle may be completed in small infarcts, though much delayed in large lesions. The fibroblasts begin to form collagen. From the *fourth* to the *sixth week* collagen formation is marked. (Plate IX.) By the *end of the second month* the process is complete and the infarct is healed. All the dead muscle is replaced by dense scar tissue, and only a few cells and granules of blood pigment remain. (Fig. 168.) The speed of the process varies with the size of the infarct and the state of the remaining circulation.

Gradual occlusion of the vessel will lead to the same end-result, *i. e.*, myocardial scarring, though without the production of an infarct. In this case the muscle fibers gradually die and are replaced by fibrous tissue, the condition inappropriately called chronic interstitial myocarditis. No blood pigment is found in these lesions. Fatty degeneration can

be demonstrated in the slowly dying fibers; this is not the case in an infarct.

It not infrequently happens that in an autopsy on a person who has had no cardiac symptoms and who has died as the result of some other disease one is astonished to find the left coronary completely blocked by atheroma. The explanation is that a collateral circulation has slowly been established. The work of Blumgart and Schlesinger has demonstrated the part played by collateral vessels in a striking way. The coronary arteries were injected with a radio-opaque lead mass of different colors, followed by combined roentgenographic and dissection studies. The right artery was colored red and the left blue. Fine

## PLATE IX



**Fibrosis of the Myocardium, the Result of Coronary Occlusion.**

The heart muscle is red, the fibrous tissue blue. (Mallory's connective tissue stain.)



anastomoses less than 40 microns in diameter exist between the two sides, but these are of no functional value and do not permit passage of the injection mass. As the result of *slow* obstruction, abundant wide anastomoses develop, so that subsequent sudden obstruction may not result in infarction because the collateral circulation keeps alive the area deprived of its normal blood supply. This explains how it is that the site of an infarct does not necessarily bear a constant relation to the site of occlusion. This anastomotic circulation develops only where and when it is needed, either as a result of diminished coronary flow, or as a result of increased demand in a heart undergoing hypertrophy.



FIG. 167.—Infarct of heart, early stage. The dark material represents normal muscle fibers, the pale areas are degenerated fibers.  $\times 200$ .



FIG. 168.—Healed infarct of heart.  $\times 140$ .

In rare cases there may be *infarction without coronary occlusion*. These cases, which are very puzzling, must be attributed to *relative* myocardial ischemia, which may be only temporary. In most of the cases hypertension has been present, a condition in which vasoconstrictor phenomena are common, and in which there is myocardial hypertrophy with a correspondingly increased demand for blood. There may be a temporary fall of the intra-aortic blood-pressure, or failure of the mechanism regulating compensatory dilatation of the coronaries. Finally, the pathologist may have failed to demonstrate occlusion of one of the smaller arteries. When the coronary vessels

are examined by the combined injection-dissection technic it is found that almost two-thirds of the occlusions are less than 5 mm. long (Schlesinger and Zoll). Such short occlusions are easily overlooked.

**Relation of Symptoms to Lesions.**—The sudden pain, distress, dyspnea, *angor animi* are due to the heart having received a sudden trauma from the cutting-off of the blood supply to part of the muscle. When any muscle is suddenly deprived of its blood supply as by embolism it goes into a painful spasm. An ordinary muscle can be rested, but the heart cannot afford to stop and rest. The leucocytosis is due to the formation of what is practically an aseptic abscess in the heart. The fever is probably in the nature of a protein reaction from the dead tissue. The pericardial friction rub is due to the presence of a patch of aseptic inflammation caused by necrosis of the muscle on the surface of the left ventricle. It is not heard in occlusion of the right coronary artery, as the affected area is on the posterior surface of the heart.

There is a growing feeling amongst clinicians that there may be some connection between gall-bladder infection and coronary thrombosis. Patients with gall-bladder disease may show symptoms of early cardiac failure or *angina pectoris*. There may be only symptoms or definite cardiac lesions may be present.

**Angina Pectoris.**—*Angina pectoris* or sudden pain in the chest is a clinical rather than a pathological entity. In its typical form it differs sharply from the clinical picture of acute coronary occlusion, for the pain in *angina* comes on as the result of sudden exertion or emotional excitement and goes off when this has passed, it tends to pass down the arms, particularly the left, and there is none of the fever and leucocytosis of infarction of the heart. In many cases, however, the pictures come closer together, and a person may have a number of attacks of *angina pectoris* and finally die of coronary occlusion. The patient may die in the first attack as in the case of Dr. Arnold of Rugby, or he may have many attacks as did John Hunter, who described one of these in the following vivid words: "As I was walking about the room I cast my eyes on a looking-glass and observed my countenance pale, my lips white, and I had the appearance of a dead man looking at himself."

It is generally believed that the pain is due to temporary myocardial ischemia, the attack being brought on by physical exertion or emotional excitement which throw an additional strain on the heart. The ischemia is relative, and may be caused not only by coronary atheroma, syphilitic aortitis, aortic stenosis, etc., but also by cardiac hypertrophy without a corresponding increase in the coronary circulation. It is evident that anginal attacks may finally terminate in cardiac infarction.

The work of Sir Thomas Lewis on pain in skeletal muscle throws a sidelight on the mode of production of myocardial pain. The circulation was cut off from the arm by means of a tourniquet, and the hand was made to work by pressing on a small instrument containing a spring. Pain began in thirty seconds and became unbearable in seventy-five seconds. If the muscle were kept at rest there was no pain. When pain was induced, the work stopped and the tourniquet kept on, the pain continued at the same level of intensity; when the ligature was removed, the pain disappeared in from two to four seconds. Lewis believes that processes arise in the muscle fibers which lead to changes in the tissue spaces around these fibers and cause the pain, which



is therefore chemical in origin. In coronary occlusion the ischemic muscle continues to work, keeping up the chemical factor in the tissue spaces; hence the gradual onset of the pain and its long duration. Amyl nitrite probably acts in angina by dilating the coronaries and sweeping away the pain-producing factor in the tissue spaces; it does less good in coronary occlusion because the occluded vessel is unable to open, and the drug can act only on the collateral circulation to the ischemic muscle.

**Sudden Cardiac Death.**—When a person dies suddenly of heart failure (instantaneously or in the course of a few minutes or hours), the cause may lie in the myocardium, the coronary arteries, or the aorta. (1) There may be rupture of the heart due either to softening of an infarct or to the formation of an aneurism of the heart at the site of a scar. Sudden death on exertion may follow the myocardial degeneration of diphtheria. (2) Coronary occlusion is the commonest cause of sudden cardiac death. The occlusion may be at the mouth of the artery as in syphilitic aortitis, or in the course of the artery as in atheroma. (3) In the aortic group may be placed rupture of an aortic aneurism, some cases of angina pectoris, and aortic incompetence. Finally there remains a group of cases in which the patient dies of sudden heart failure, but no satisfactory cause can be found at autopsy. Such cases may be put down to shock, status lymphaticus, or a visitation from God.

**Myocardial Degenerations.**—The myocardial fiber is a specialized cell, and is therefore subject to the usual degenerative changes from which cells suffer. In septicemia and toxemias the heart may be so flabby that it flops down on the autopsy table. This extreme lack of tone, not necessarily associated with any microscopic change and difficult to designate with a fitting name, may be the only structural alteration in the entire body, and may with justice be blamed as the immediate cause of death.

**Cloudy Swelling.**—This is a condition of slight importance, and difficult to differentiate from postmortem autolytic change. It is seen after infectious fevers, especially typhoid, septicemias, etc. The heart is softer and paler than normal. The fibers are swollen and contain granules soluble in weak acetic acid.

**Fatty Degeneration.**—This is caused by the usual factors responsible for fatty degeneration (see Chapter II), of which severe anemia, especially the pernicious form, is the chief. In the gross the heart shows the characteristic mottled “thrush-breast” appearance, best seen under the endocardium covering the papillary muscles of the left ventricle. (Fig. 169.) The yellow spots represent areas of fatty change. Microscopically rows of fat droplets are seen in the muscle fibers in frozen sections; they can be stained red with Sudan III or Scharlach and black with osmic acid. Unless it is very extreme the condition does not seem to interfere seriously with the power of the heart.

**Fatty Infiltration.**—This is a lipomatosis of the heart, with deposits of fat under the pericardium and in the interstitial tissue. (Fig. 170.) It is merely part of a general adiposity. The muscle fibers may suffer

from pressure, and if the infiltration is very marked there may be interference with the heart's action.



FIG. 169.—Fatty degeneration of the heart. The "thrush breast" appearance is well shown. From a case of profound anemia.



FIG. 170.—Fatty infiltration of heart.  $\times 125$ .



FIG. 171.—Fragmentation of myocardium.  $\times 250$ .

**Brown Atrophy.**—Here there is wasting of the heart, which is of a deep brown color. The condition is seen in long-continued wasting diseases and in old age. The muscle fibers are small, and at each pole of the nucleus there is a collection of yellow pigment, one of the lipochromes. This pigment has been well named a “wear-and-tear” pigment, for, although normally present in small amount, it becomes very greatly increased in conditions where the tissues undergo much wear and tear.

**Deficiency Disease.**—In vitamin deficiency, especially deficiency in vitamin B<sub>1</sub>, there may be symptoms of myocardial failure. These patients are usually chronic alcoholics (alcohol having high caloric value but no vitamin B<sub>1</sub>), food cranks or drug addicts. In a group of such cases Weiss and Wilkins found hydropic degeneration of the myocardium and conduction fibers and an increase in intercellular tissue. Thomas and his associates fed rats and hogs on a diet deficient in mineral and vitamin (potassium and vitamin B<sub>6</sub>) and produced severe myocardial necrosis, cellular infiltration and later fibrosis.

**Fragmentation.**—In soft and flabby hearts, such as occur in continued infections, intestinal obstruction, etc., the muscle fibers may be fragmented, *i. e.*, broken across transversely, the broken ends being separated for some little distance (Fig. 171). Owing to the absence of any surrounding reaction to injury it is usually supposed that the condition develops in the death agony. It may occur in the healthy heart if death is violent (hanging, strychnine poisoning, etc.). In the latter cases there is likely to be a clean break and nothing more, whereas in the flabby hearts there is often an accompanying degeneration and disintegration of the muscle fibers.

**Tumors of the Heart.**—Primary tumors of the heart are very rare, and need only be mentioned. Myxoma is a soft pedunculated tumor growing from the wall of the left auricle at the site of the closed foramen ovale. (Fig. 172.) The surface may be papillary in character. The microscopic picture is myxomatous, but may suggest that the tumor is really an endothelioma. Fibroma, angioma, and rhabdomyoma have been described. The rhabdomyoma is a developmental tumor which is associated with tuberous sclerosis of the brain and developmental defects in the kidneys. Secondary growths are more common, particularly malignant melanomas.

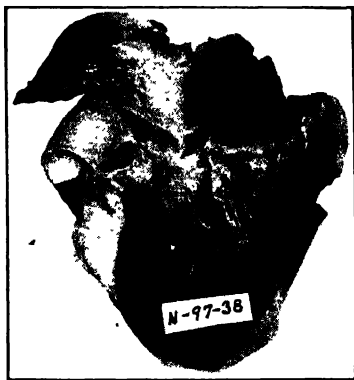


FIG. 172.—Myxoma of heart growing from wall of left auricle.

## CONGENITAL HEART DISEASE

A great variety of congenital abnormalities of the heart may occur, some very rare, others incompatible with life, *e. g.*, absence of the heart, ectopia cordis, displacement of the heart in the neck or the abdomen, etc. There may be minor defects such as a lacunar fenestration of the semilunar valves, which are of no functional significance. Only the commoner conditions will be touched on here. For a fuller account the writings of Maude Abbott should be consulted.

The key to most of the defects lies in variations in the formation of the septum which divides the heart into a right and left side. The primitive heart consists of three chambers, auricle, ventricle, and aortic bulb. Separate septa are formed which divide these chambers longitudinally into right and left sides, and subsequently fuse. If anything goes wrong with this fusion, congenital defects will result.

While the septum which divides the aortic bulb into aorta and pulmonary artery is being formed, a spiral twisting occurs so that the pulmonary artery moves forward and to the right, the aorta backward and to the left. If this twisting does not take place the aorta will rise from the right ventricle and the pulmonary artery from the left. This condition is known as *transposition of the great vessels*.

Much commoner is a *deviation of the septum*, nearly always to the right, so that the pulmonary artery is narrower and the aorta wider than normal. In this way pulmonary stenosis is produced. The bulbar septum is now unable to fuse with the ventricular septum, and the root of the aorta is astride of the latter so as to arise partly from the left and partly from the right ventricle. A gap remains in the upper or membranous part of the interventricular septum.

Even if the deviation of the bulbar septum is not sufficient to bring the aortic opening astride of the ventricular septum, the upper part of that septum will still tend to remain open, for the narrowing of the pulmonary opening raises the pressure within the right ventricle so that the blood tends to flow from it into the left ventricle, thus interfering with the closure of the opening in the interventricular septum. The same holds true for closure of the interauricular septum and the ductus arteriosus which connects the pulmonary artery with the aorta in intra-uterine life. It is for this reason that pulmonary stenosis is so often associated with other congenital cardiac defects. Deviation of the septum to the left will cause stenosis of the aortic opening, a much rarer condition.

The various congenital cardiac anomalies may be divided into two great groups: (1) Those in which there is an arteriovenous shunt with intermingling of the blood in the systemic and pulmonary circulations, and (2) those in which no such communication exists. Cyanosis, which is so important a symptom of congenital heart disease, is only present when blood flows from the right side of the heart into the left (venous-arterial shunt). This may occur if the septal defect is large, if the pressure on the right side is raised by pulmonary stenosis or failure of the left ventricle, or if the aorta arises partly from the right ventricle. The flow may originally be from left to right, but when left-sided failure sets in the direction of flow may be reversed. It may be noted that even the most extreme degree of cyanosis is not associated with edema, a highly characteristic feature.

Congenital defects are points of weakness against bacterial infection. Not infrequently the patient with congenital heart disease dies of sub-acute bacterial endocarditis. The vegetations may be found on a

bicuspid aortic valve, a stenosed pulmonary valve, or at the site of coarctation of the aorta.

**Pulmonary Stenosis.**—This is the most important of the congenital heart lesions. Though associated with marked cyanosis the condition is compatible with fairly long duration of life. The opening is narrowed, and in addition the cusps are commonly fused together to form a diaphragm in the center of which there is a circular opening. The valve is usually sclerosed, but may be of normal thickness. Instead of three cusps there may be two or four. The wall of the right ventricle shows a marked work hypertrophy. In rare cases the stenosis may be either proximal or distal to the valve. The condition may be associated with patent foramen ovale, deficient interventricular septum, and patent ductus arteriosus. The usual cause of the condition is a deviation of the bulbar septum to the right, so that an unduly small pulmonary artery is cut off from an unduly large aorta with the production of the *tetralogy of Fallot*, *i. e.*, pulmonary stenosis, displacement of the aorta to the right, enlargement of the right ventricle, and a defect in the interventricular septum. It is possible, though by no means certain, that a small number of cases are due to fetal endocarditis. Those cases in which the valves are sclerosed and adherent, but without any accompanying displacement of the aorta or defect in the interventricular septum, may be inflammatory rather than developmental in origin.

The diagnosis of pulmonary stenosis can now be made during life with a high degree of accuracy. In addition to such features as marked cyanosis (the classical "blue baby"), compensatory polycythemia, low oxygen content of the peripheral blood, and severe dyspnea, the roentgenogram reveals the same size of the pulmonary artery.

From what has already been said it is evident that the condition of the ductus arteriosus is all-important, for it is by this route that the lungs receive their main blood supply. If partial closure of the ductus occurs, the condition of the child may become extreme or desperate. For the relief of such a condition Blalock and Taussig have devised an operation which has succeeded in restoring the circulation to normal and the child to health. The principle is to bypass the obstruction by constructing an artificial ductus arteriosus, so that an adequate supply of blood is poured into the pulmonary circulation. This is done by anastomosing the innominate or left subclavian artery to the right or left pulmonary artery just distal to the bifurcation of the main artery in such a way that the blood flows to both lungs. In many instances the most dramatic improvement has resulted. The most suitable cases are those presenting the tetralogy of Fallot with a small or closed ductus. Owing probably to the polycythemia there is a marked tendency to thrombosis, particularly in the cerebral vessels, and this may lead to a fatal termination after, and occasionally before, operation.

**Aortic Valve Lesions.**—Aortic stenosis is much less common than pulmonary stenosis. Apart from stenosis there may be an abnormal

number of cusps, two or four. A bicuspid aortic valve is peculiarly liable to suffer from subacute bacterial endocarditis. Gross points out that if a bicuspid aortic valve is really congenital in nature it will be associated with other developmental cardiac defects; such cases are usually seen in children. In adults the condition is usually acquired in nature, rheumatic in origin, and not associated with other defects.

**Coarctation of the Aorta.**—This is a condition of narrowing of the aorta (*coarctare*, to press together) in the region where it is joined by the ductus arteriosus. Two forms are recognized, the infantile and adult, depending on the relation of the constriction to the ductus. In the *infantile type* the constriction is proximal to the ductus, between



FIG. 173.—Coarctation of aorta with collateral circulation. (Maude Abbott and Dawson, *International Clinics*, courtesy of J. B. Lippincott Company.)

it and the subclavian artery, and the ductus remains widely patent. Other cardiac anomalies are common in this form. In the *adult type* the constriction is at or just distal to the ductus, which is obliterated. Other anomalies are rare, but subacute bacterial endocarditis is a common cause of death. The infantile form is not compatible with continued life, and is found in the still-born and young infants. The narrowing may be so great that the opening may barely admit a probe. In the adult form the blood makes its way to the lower part of the body by means of greatly dilated collateral vessels, the subscapular and internal mammary arteries from the subclavian anastomosing with the intercostals and epigastrics respectively. (Fig. 173.) This collateral circulation fails to develop in the infantile type, as the blood from the patent ductus enters the aorta

beyond the obstruction. The *clinical picture* is characteristic, *i. e.*, arterial hypertension in the upper part of the body, large pulse volume in the arm and small in the leg, palpable or visible vessels along the dorsal border and angle of the scapula (subscapular collaterals), and a grooving of the ribs in the roentgen-ray film (internal mammary and intercostals).

It is now possible to excise the stenosed segment and join the divided ends. After this surgical *tour de force* the clamps on the aorta must be released gradually, otherwise the sudden release of pressure may lead to fatal fibrillation of the left ventricle.

**Patent Ductus Arteriosus.**—The ductus arteriosus is the channel by which in intra-uterine life the blood passes from the right heart into the aorta without passing through the lungs. It arises at the bifurcation of the pulmonary artery and ends in the aorta beyond the opening of the left subclavian artery. It is patent at birth, but becomes obliterated

during the third and fourth weeks of extra-uterine life. It often remains open as the result of other congenital defects.

When the ductus remains patent, a condition which is twice as common in females as in males, the blood flows from the aorta into the pulmonary artery. In uncomplicated cases, therefore, there is no cyanosis. There may, however, be a temporary reversal of flow owing to heightened pulmonary pressure, as in prolonged crying, violent physical exertion, or terminal heart failure, with resulting cyanosis. If the ductus is acting as a compensatory mechanism to other congenital cardiac anomalies, cyanosis may be present even under resting conditions. There may be a rumbling systolic murmur and thrill in the pulmonary area. It is possible to pass a tube into a vein in the arm, and onwards into the jugular vein, right auricle and ventricle, finally entering the pulmonary artery. By this means the pressure effect of the flow of arterial blood into the pulmonary artery can be demonstrated and the increased oxygen content of the blood can be determined, so that the diagnosis can be confirmed with absolute certainty.

Although the condition is compatible with a long and active life, in the great majority of cases life expectation is considerably shortened. The great danger is the development of *Streptococcus viridans* endarteritis. This threat can now be averted by ligation of the ductus, or even better, by complete division.

**Deficiencies of the Septa.**—In rare cases the septum between the auricles or the ventricles may be absent. The condition is not compatible with life. Incomplete closure is much commoner.

**Interauricular Communication.**—The foramen ovale remains patent in about 25 per cent of normal persons, but, as the opening is usually very small and oblique or valvular, little blood can pass from one side to the other. It may be widely patent, and yet give rise neither to signs nor symptoms. Even the cyanosis so common in congenital heart disease is absent, for the blood merely passes from the left to the right auricle and thence to the lungs where it is oxygenated.

**Interventricular Communication.**—The deficiency of the septum which may occur in pulmonary stenosis has already been described. In addition there may be an opening in the membranous part of the septum or in the muscular wall immediately in front of it (Roger's disease). The heart is large and globular, and a loud systolic murmur is heard and a systolic thrill felt at the inner end of the third left intercostal space.

**Relation of Symptoms to Lesions.**—The chief symptom is cyanosis. This may be present at birth ("blue baby"), or may develop later. It is due to the venous blood on the right side mixing with the arterial blood on the left. A compensatory polycythemia or increase in the number of the red blood cells takes place so as to compensate for the deficiency of oxygen. The size of the erythrocytes is also increased, so as to average 8 microns or more. Dyspnea is a common symptom due to deficient oxygenation. The patient is small and puny. There is clubbing of the fingers, as often happens in conditions of poor oxygenation; the terminal phalanges are thickened and the nails thick and curved. Various murmurs and thrills may be detected, but none are pathognomonic. The absence of pulsation in the lower extremities in coarctation of the aorta is very characteristic.

## THE PERICARDIUM

**Pericarditis.**—Inflammation of the pericardium is usually rheumatic in origin, and forms part of a rheumatic carditis. The pneumococcus is the next commonest cause, spreading from a pneumonic lung to the pericardium by way of the lymphatics. It may occur as a complication in septicemia or any of the infectious fevers. The tubercle bacillus may be the infecting agent. Finally it may be a terminal condition in chronic debilitating diseases, particularly Bright's disease (uremic pericarditis).

**Symptoms.**—The chief clinical features are fever, precordial pain, and a friction rub which at first may be soft like the rustling of silk, but later is rough and rasping like the creaking of leather. No acute infection may be more insidious in onset than pericarditis, and there may be no fever, no pain, no friction. Often the condition is discovered for the first time at autopsy, to the great surprise of the clinician.



FIG. 174.—Acute pericarditis. The shaggy nature of the exudate is well shown.

**Lesions.**—The pericardium shows the usual characteristics of inflammation of a serous membrane. A thick fibrinous deposit is laid down on both the visceral and parietal layers, giving the heart a shaggy ("bread-and-butter") appearance. (Fig. 174.) Its gross and micro-



scopic characters have already been described in connection with rheumatic heart disease. There is a varying amount of serous exudate, scanty in the rheumatic form but abundant and sometimes purulent in pneumococcal and other infections. The fluid collects first at the base of the heart. The fibrinous exudate may be largely absorbed, but some of it may be organized by the ingrowth of fibroblasts, and opaque white patches or *milk-spots* are left usually on the anterior surface of the right ventricle. Organization of the exudate may lead to the formation of adhesions between the two surfaces, and these may involve the whole heart, a condition known as adherent pericardium. Calcification may occur in the organized tissue with the formation of stony plates on the surface of the heart.

**Relation of Symptoms to Lesions.**—The most characteristic physical sign, the friction rub, is due to the two roughened surfaces rubbing against one another. If fluid accumulates to any extent the surfaces may be separated and the friction disappears. If the fluid is very abundant the heart sounds will be faint and distant. The pain is due to the same cause as the friction, the rubbing together of the inflamed surfaces. It may be slight or absent, and disappears as the fluid accumulates.

**Tuberculous Pericarditis.**—The heart is usually covered with a fibrinous exudate which completely conceals the tubercles. The effusion is generally very abundant and purulent. If a pericardial sac is distended with pus, the condition is likely to be tuberculous or pneumococcal. Hemorrhage is common. A bloody exudate should suggest either tuberculosis or malignant disease. Microscopically the characteristic tubercles are seen under the fibrinous exudate.

**Chronic Constrictive Pericarditis.**—In this uncommon condition the heart is compressed by a layer of dense tough fibrous tissue which envelops the organ. There is great uncertainty as to the cause of the dense envelope. Rheumatism can be ruled out. In healed rheumatic pericarditis the scar tissue is thin, the fibers are slender, chronic inflammatory cells are present, and there is no extensive destruction of tissue. In constrictive pericarditis the thick, dense envelope may present large cavities containing inspissated caseous material. The tissue is hyalinized, any collagen fibers are huge, calcification is common, and tissue destruction is marked. It seems probable that most cases are tuberculous, although complete healing may have occurred.

The compression prevents the normal diastolic filling of the auricles, so that there is marked distention of the jugular veins, marked enlargement of the liver and recurring ascites. The heart, although profoundly disabled, is characteristically small and quiet, because it is unable to dilate or hypertrophy. The liver and spleen may be coated with a layer at first fibrinous and later fibrous, the so-called sugar-icing (*Zuckerguss*). This is apparently due to the long-standing ascites. The pleura may be similarly involved. This polyserositis has been called *Pick's disease*. Resection of the thickened and constricting pericardium has given excellent results in many cases.

**Hemopericardium.**—Hemorrhage into the pericardial sac may be due to rupture of the heart, wounds of the heart, or rupture of an aneurism of the first part of the thoracic aorta. If the hemorrhage is rapid it will compress the auricles so that they cannot be filled, and death occurs from heart failure. If the hemorrhage is only a slow leak the heart may accommodate itself to the pressure. Blood is often found in the fluid exudate in tuberculous pericarditis and in effusion due to secondary tumors of the pericardium. Petechial hemorrhages in the serous membrane are common in septicemic and anemic conditions.

**Hydropericardium.**—This is a dropsy of the pericardial sac, usually part of a general dropsy due to cardiac or renal disease. The sac may be greatly distended with clear watery fluid, which may interfere seriously with the heart's action.

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## CHAPTER XVI

### THE BLOODVESSELS

#### THE ARTERIES

FOR the purposes of pathology it is convenient to divide the arteries into three classes: (1) The large or elastic type (aorta, carotid, etc.); (2) the medium or muscular type (radial, renal, superior mesenteric, etc.); (3) the intimate vasculature (small vessels such as the interlobular arteries and afferent arterioles of the kidneys). The distinction is useful, because each of these suffers from a different form of degenerative lesion; in the elastic type atheroma is the common lesion, in the muscular type the medial sclerosis of Mönckeberg, and in the intimate vasculature the diffuse hyperplastic type of sclerosis. Exceptions to this generalization will be encountered (*i. e.*, atheroma in small vessels such as the coronaries and cerebrals), but the generalization is useful nevertheless. Arterial lesions will be divided into three main groups for descriptive purposes: (1) Inflammatory lesions such as acute arteritis, syphilis, and rheumatism; (2) obliterating lesions such as thrombo-angiitis obliterans, periarteritis nodosa, and obliterating endarteritis; (3) the degenerative arteriosclerotic group, *i. e.*, atherosclerosis, Mönckeberg's medial sclerosis, and diffuse hyperplastic sclerosis. It must be remembered that the postmortem appearance does not necessarily represent the true condition of the artery during life. The small lumen and deeply folded intima and internal elastic lamina are due to contraction of the media after death, and will naturally vary with the amount of contraction. These artefacts are a fallacy which invalidates much of the work of measuring arterial walls and lumina.

#### ACUTE ARTERITIS

**Acute Periarteritis.**—Acute inflammation may attack an artery from the outside or the inside. An artery which passes through a focus of suppuration such as an abscess should be very liable to infection, but on the contrary it is quite resistant. Sometimes, however, the bacteria penetrate the wall and produce an acute arteritis and periarteritis, the media and adventitia being filled with polymorphonuclear leucocytes. The wall may be so weakened that hemorrhage may occur. Before the days of asepsis *secondary hemorrhage* was very common in operation wounds and was due to an acute suppurative arteritis produced by the septic ligature which was buried in the lacerated wall of the vessel. After a number of days the destruction of the wall was so great that hemorrhage occurred into the wound, and this was often fatal.

**Acute Endarteritis.**—If an infected embolus from a septic thrombus in a vein or a vegetation of an acute endocarditis lodges in an artery it infects the vessel from within. Again the vessel wall becomes acutely inflamed. The results may be (1) septic thrombosis with breaking up of the thrombus and the formation of secondary metastatic abscesses; (2) the production, by weakening of the wall, of a small mycotic aneurism. This may burst and lead to severe or fatal hemorrhage.

### SYPHILIS OF THE ARTERIES

Syphilis attacks two important sets of vessels: (1) the aorta and its large branches, and (2) the cerebral arteries. Other vessels may be affected, but the clinical effects are of relatively little importance compared with these two.

**Syphilitic Aortitis.**—Aortitis is one of the commonest and most important of syphilitic lesions. It is usually found in males between the ages of thirty and fifty-five years. Symptoms seldom appear within five years of the primary lesion, although the aorta is probably infected from the very beginning of the disease. The spirochetes are lodged in the adventitia and media and are remarkably resistant to treatment, with the result that active lesions can almost always be found at autopsy, no matter how vigorous the treatment has been.

**Symptoms.**—The chief symptom is substernal pain. With the progress of time an aortic aneurism may develop, a condition which will be considered later.

**Lesions.**—The *gross appearance* is very characteristic unless it is obscured by the development of atheroma. The lesion begins in the aortic wall just distal to the aortic cusps, and spreads horizontally around the root of the aorta and distally as far as the mouths of the great vessels springing from the arch. This forms in many cases a zonal lesion picturesquely known as the girdle of Venus. Even more frequently the whole arch is diffusely involved. The probable reason why the suprasigmoid portion is the site of election is that it has such an abundant lymph supply, the spirochetes being carried in the perivascular lymphatics. The gross changes may be traced down as far as the diaphragm, where they suddenly stop, and as a rule the abdominal aorta is free from lesions.

In the affected area the intima is raised into patches, at first smooth and pearly, but later pitted and scarred. The intervening tissue is wrinkled like the bark of a tree. Longitudinal wrinkling is striking, but is not specific. It is the fine transverse wrinkling due to stellate scars which is highly characteristic of syphilis. The swelling of the intima may so narrow the openings of the coronary arteries that they are reduced to mere pin-points or one of them may be completely closed. In such a case there may be symptoms of coronary obstruction or the patient may suddenly drop dead. The disease does not spread along the coronary arteries. In a pure case the yellow fatty changes,

calcification and ulceration of atheroma are absent, but it must be remembered that atheroma of the aorta often complicates syphilis. The adventitia is thickened, and the vessel is often unduly adherent to the mediastinum. The cut edge shows thickening both of the intima and the media. Owing to destruction of the elastic tissue by the spirochetes there is a dilatation of the vessel and especially of the aortic ring. In this way an extreme degree of aortic incompetence may be produced, for the cusps are quite unable to come together.

The condition of the *aortic valve* deserves close attention. In some cases the cusps are quite normal, even though there is a marked degree of incompetence. In other cases a characteristic condition of *syphilitic endocarditis* is present. This never occurs apart from syphilitic aortitis, and is never seen in the mitral valve. There are two distinctive lesions (Fig. 175): (1) the cusps are sclerosed and contracted, and the free

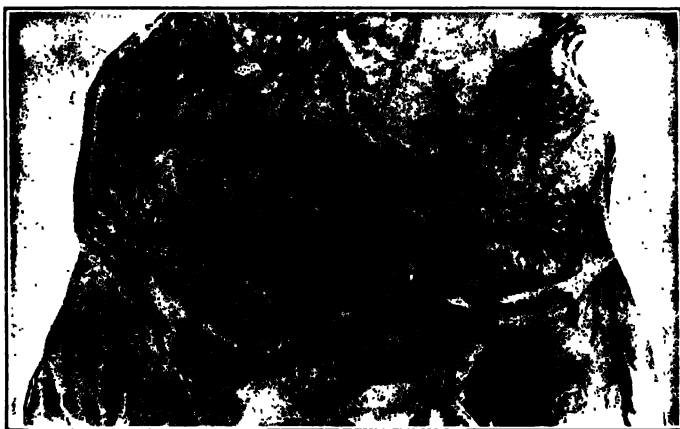


FIG. 175.—Syphilitic aortitis. The surface of the aorta is nodular, wrinkled, and scarred. There is widening of the commissure, and thickening of the free margin of the aortic cusps.

edge shows a peculiar cord-like thickening quite unlike that seen in any other form of endocarditis. (2) There is a widening of the commissure, *i. e.*, a separation of the cusps at the point where normally they should meet, as if a wedge of tissue had been forced between each pair. The infection has evidently extended into the valve from the aortic wall, and the central part of the cusps is the least affected.

The *microscopic picture* is that of a periarteritis and mesaortitis with secondary changes in the intima. The earliest change is in the adventitia in the form of masses and linear streaks of lymphocytes and plasma cells. (Fig. 176.) These are collected round the vasa vasorum, owing to the distribution of the spirochetes in the perivascular lymphatics. The vasa vasorum normally penetrate only the outer third of the media but the spirochetes stimulate them to grow and branch so that they invade the whole thickness of the media. This is associated with

fibroblastic proliferation and marked fibrous overgrowth of the intima which later becomes hyaline. The infection spreads into the media where there are foci of inflammatory cells, necrosis, and extensive destruction of the elastic tissue. It is the *mesaortitis* which is the most serious part of the disease, because with destruction of the elastic tissue the aorta loses its resiliency and either undergoes a general dilatation or develops an aneurism. New capillaries are formed which pass far into the media. The necrotic material is replaced by scar tissue. It is the contraction of this scar tissue which gives rise to the characteristic wrinkling seen on the inner surface, so that the wrinkling is naturally a late phenomenon.



FIG. 176. Syphilitic aortitis. A linear collection of inflammatory cells at the junction, of media and adventitia.  $\times 100$ .

**Relation of Symptoms to Lesions.**—The substernal pain is probably due to inflammation of the tissue at the root of the aorta. The destruction of elastic tissue and loss of elasticity may cause either general dilatation of the thoracic aorta as shown in the roentgen-ray picture, or the local dilatation known as an aneurism. Symptoms of coronary occlusion and even sudden death may be caused by closure of the openings of the coronary arteries by plaques of thickened intima. The three great dangers of syphilitic aortitis are: (1) aortic incompetence (the commonest), (2) stenosis of the coronaries, and (3) aneurism.

**Syphilitic Arteritis.**—This is best seen in the central nervous system in the small arteries of the meninges and the vessels at the base of the brain. The lesion is both a periarteritis and an endarteritis. (Fig. 177.) As the spirochetes are in the lymphatics of the adventitia, the vessel is surrounded by a mantle of lymphocytes and plasma cells. There is some atrophy of the media, but this is not an important lesion. The

intima shows a marked uniform thickening with great narrowing of the lumen, an endarteritis obliterans, quite different from the patchy atheroma which often affects these vessels. The narrowing of the lumen is apt to lead to thrombosis and cerebral softening. There is no relation between syphilitic arteritis and either aneurism or hemorrhage as is commonly supposed, for the thickened vessel is not weakened in one spot as it is by a patch of atheromatous degeneration. As the infection dies out the arteries become sclerosed and stiff, and have been likened to macaroni.



FIG. 177.—Syphilitic endarteritis of basilar artery, showing uniform thickening of the inner coat and thickened internal elastic lamina (elastic tissue stain).

**Rheumatic Aortitis.**—The lesion is similar to that produced by syphilis, but much less marked in degree. Definite rheumatic nodules (Aschoff bodies) may be formed in the adventitia, but usually there are merely collections of lymphocytes and plasma cells around the vasa vasorum in the adventitia and to a lesser degree in the media together with a few large cells of the Aschoff type. The damage to the media is slight compared with that produced by syphilis and the lesion does not appear to be a factor in aneurism formation.

**Rheumatic Arteritis.**—The visceral vessels may show very characteristic lesions first described by von Glahn and Pappenheimer. These lesions may occur in the arteries of the lung, kidney, pancreas, ovary and testicle. The lesion is a panarteritis, all the coats being involved. (Fig. 178.) The wall is filled with an inflammatory exudate containing much fibrin, so that it is much thickened. Around the vessel there is a peculiar exudate composed of mononuclear cells the nuclei of which are strangely compressed and elongated, together with some polymorphonuclear leucocytes. The most remarkable feature is the subsequent vascularization of the damaged wall; new capillaries are formed in the wall so that the original lumen is surrounded by spongy vascular tissue. There is no thrombosis, so that the lesions do not injure the parts supplied by the vessels involved. In rheumatic fever the coronary arteries may show a severe exudative and necrotizing arteritis involving all the coats.



In inactive cases the smaller branches of the coronaries may present proliferation of the fibrous and elastic tissue resembling that of arteriosclerosis, but occurring at an earlier age.

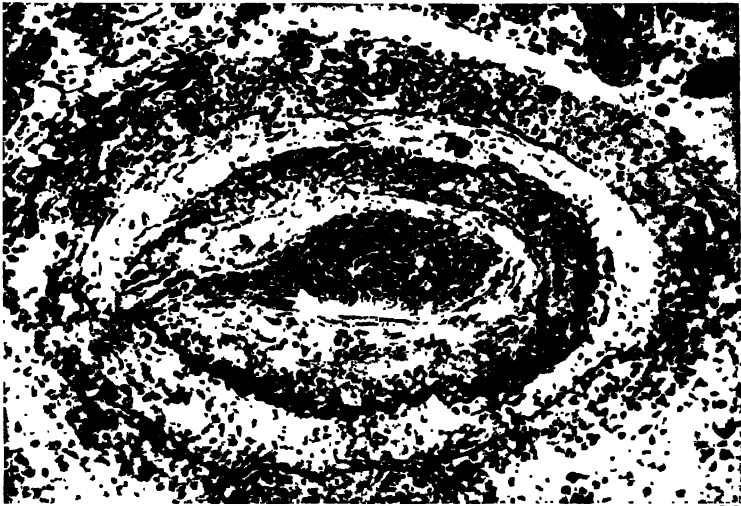


FIG. 178.—Vascular lesion in rheumatic fever. Great thickening of the inner coat, and infiltration of all the coats by inflammatory cells.  $\times 200$ .

### THROMBO-ANGIITIS OBLITERANS

This remarkable condition is often called Buerger's disease, because it was Buerger who first recognized that the lesion was an inflammation of the wall with resulting thrombosis, and not a degenerative thickening of the intima allied to arteriosclerosis, as used to be thought. The symptoms are not due to the active disease but to the after-effects which develop in the chronic stage. The acute stage is rarely seen by the pathologist, so that he is apt to get a very erroneous and one-sided idea of the process.

The sex incidence is striking, for the disease is practically confined to men, although cases in women are now being reported. The race incidence, though also striking, is less extreme. In North America it is usually seen in young Russian and Polish Jews, but Gentiles may also suffer and even Scotsmen are not immune. It is a disease of young adult life. The lesions are usually in the vessels of the legs, but the arms may also be affected, sometimes exclusively.

The cause is unknown, but is usually considered to be bacterial in nature. Non-hemolytic streptococci have been found in the blood, and injection of these bacteria into sites adjacent to the femoral vessels has reproduced the disease in rabbits; a similar result is obtained by embedding segments of diseased human arteries alongside the femoral vessels (Horton and Dorsey). A surgeon who pricked his finger with a spicule of bone when amputating the leg in a case of

Buerger's disease subsequently developed characteristic lesions in the digital arteries of the injured hand. The excessive use of tobacco, especially cigarettes, has long been added by clinical observers to such factors as sex, race and age. The work of Sulzberger supports this idea. As a result of observations with the patch skin test he came to the conclusion that a large majority of patients suffering from this disease were hypersensitive to tobacco proteins, although not to nicotine itself. Allergic reactions may produce necrosis, and this may lead to aseptic inflammation. It has been suggested, though on rather insufficient evidence, that chronic typhus infection may play a part. It is probable that more than one exciting factor may be capable of producing the lesions in those who by race, sex and possibly heredity have predisposed vascular tissues.

**Symptoms.**—In the acute stage there are usually no symptoms, but there may be red and painful spots which last about a week due to a migrating phlebitis in the superficial veins of the leg. The first symptoms are usually indefinite pains in one foot or cramp-like pains in the calf after walking a short distance, a condition known as intermittent claudication (*claudicare*, to limp). No pulse can be felt at the ankle. When the foot hangs down it becomes bright red (erythromelia) and throbs painfully. When the foot is raised it becomes more blanched than normally. Later in the disease trophic disturbances appear in the form of ulcers and gangrene of the feet. The formation of trophic ulcers is often accompanied by excruciating pain, and suicide is not an uncommon termination of this distressing disease.

**Lesions.**—The *acute lesions* are only likely to be seen if the superficial vessels are excised in the acute stage (migrating phlebitis). The media and adventitia are invaded by polymorphonuclear leucocytes and so is the perivascular tissue. Both arteries and veins are involved. There is an arteritis and periarteritis, a phlebitis and periphlebitis. Only a segment of the vessel is involved, but this segment may be short or long. Thrombosis occurs in the inflamed segment, with occlusion of the lumen. The clot may contain foci of polymorphonuclears or of endothelial cells and foreign body giant cells.

The *chronic lesions* are those seen when the leg is amputated for gangrene months or years later. All signs of active inflammation has disappeared, and artery, veins, and nerves are bound together in a dense mass of fibrous tissue. The clot has become organized and converted into fibrous tissue, and there is no sign of the original lumen. (Fig. 179.) New vascular channels lined by endothelium are formed in the fibrous mass, so that the lesion is often mistaken for a mere thickening of the intima, an endarteritis obliterans. Thickening of the elastic tissue, both internal and external is a striking feature. There is no calcification, so that the vessel throws no shadow in the roentgen-ray picture.

**Relation of Symptoms to Lesions.**—The symptoms are due to loss of the peripheral blood supply or to disturbances of the collateral circulation which is set up. The prognosis depends on the extent to which the collateral circulation can be established, and modern methods of treatment are directed to the encouragement of this circulation. The cramp-like pains in the muscles are

due to the painful spasm which accompanies an insufficient blood supply when the muscle is in a state of activity. The flushing of the foot when it hangs down and its blanching when elevated is due to loss of vasomotor control, the nerves in the periadventitial tissue being involved in the inflammatory and sclerotic process. The trophic lesions may be due to a similar cause, a view supported by the fact that when the affected segment of vessel is resected the trophic lesions may heal quickly and permanently (Leriche).

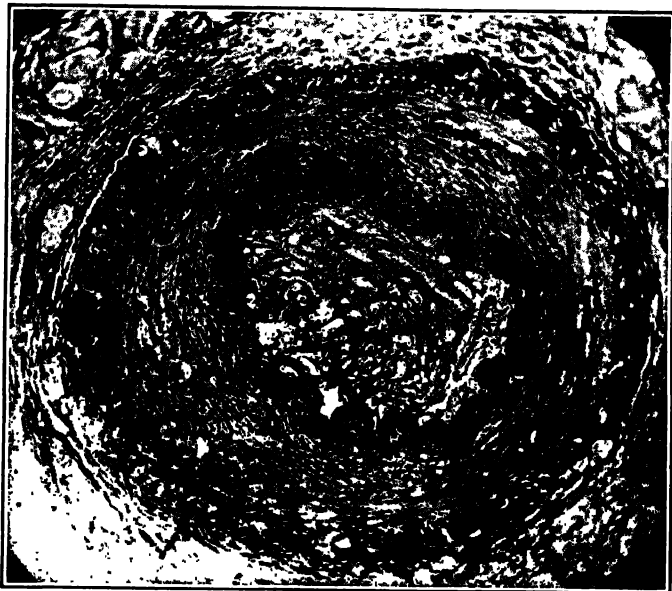


FIG. 179.—Thrombo-angiitis obliterans. The lumen is closed by fibrous tissue which is partially canalized. Hypertrophy of elastica. Elastic tissue stain.  $\times 40$ .

**Periarteritis Nodosa.**—This is a rare inflammatory disease of arteries, much more acute in type than thrombo-angiitis obliterans, and affecting the visceral vessels rather than those of the limbs. The cause is unknown, but it is not unlikely that the disease represents an anaphylactic type of hypersensitivity. The very widespread character of the lesions is in favor of this idea, and also the fact that periarteritic lesions have been found in a number of cases of serum sickness and hypersensitiveness to sulphonamides. Rich has reported a series of such cases, and has succeeded in producing diffuse periarteritis nodosa experimentally by establishing in rabbits a condition analogous to serum sickness in man.

**Symptoms.**—The disease runs an acute course with fever, prostration, sweating and loss of weight, usually ending fatally in the course of a few weeks. The symptoms are extremely varied, because vessels in almost any organ may be involved. This complex symptomatology, corresponding to no system disease, may itself suggest a correct diagnosis. A moderate increase in the eosinophils of the blood often confirms the diagnosis.

**Lesions.**—The principal vessels affected are those of the gastro-intestinal tract (mesenteric and celiac axis), the kidney and the heart, but the brain, lungs and skin may also be involved. The name is misleading, for the lesion is a panarteritis rather than a periarteritis, and in my experience most of the cases fail to show the "nodosa" feature. This term indicates the presence of small inflammatory nodules scattered along the artery like peas in a pod.

There may be hundreds of these nodules on the mesenteric vessels. The adventitia and media are infiltrated with polymorphonuclear leucocytes and there is extensive necrosis, as a result of which multiple aneurisms are formed. (Fig. 180.) Many of the nodules are really small mycotic aneurisms. The intima is also involved, so that thrombosis is common, and small infarcts are produced in the heart, kidney and other organs.

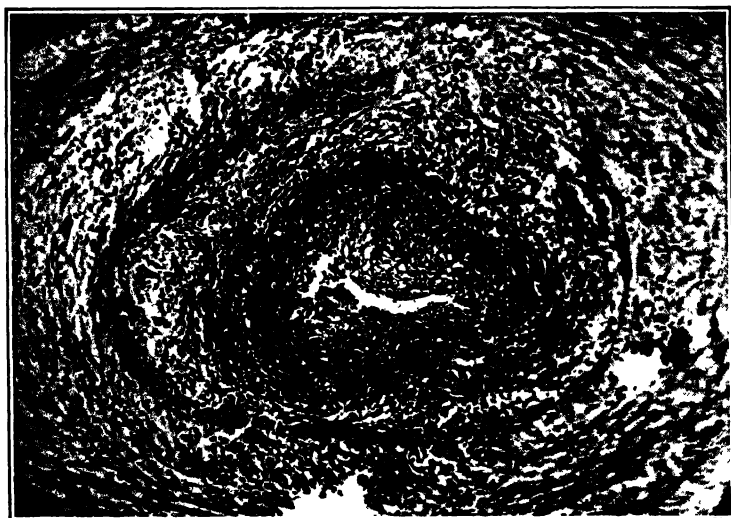


FIG. 180.—Periarteritis nodosa. All the coats of the vessel are infiltrated by inflammatory cells.  $\times 80$ .

The disease usually runs a rapidly fatal course, but it may be of more subacute type, ending up as *healed periarteritis nodosa*. This produces a clinical picture of great complexity based on multiple chronic ischemic lesions. Autopsy may reveal contracted kidneys, coronary occlusion, myocardial scars, hepar lobatum, atrophy of adrenals and pancreas, etc.

There may be acute abdominal symptoms due to involvement of the mesenteric arteries, acute cardiac symptoms from coronary artery involvement, muscular pains simulating myositis or trichinosis, etc. Neuritic pains are common; they are due to lesions of the peripheral nerves (Kernohan and Woltman). Death is often due to a ruptured aneurism. In the healed stage the symptoms will be those of ischemic sclerotic lesions of the heart, kidneys, etc.

**Temporal Arteritis.**—This condition, first described by Horton, Magath and Brown in 1932, is a chronic inflammatory process involving the temporal arteries of elderly persons, but extending to the arteries of the scalp and face. The vessels can be felt as cord-like swellings. Cooke and his associates have shown that, whilst the name is conveniently descriptive, the lesions are by no means confined to the temporal arteries, and may involve also the aorta, radial, subclavian, femoral, coronary, renal, mesenteric, and retinal arteries. The inflammation appears to spread from the adventitia to the media. The walls of the vessels are thickened and thrombosis is common. Foreign body giant cells have been described in some cases and eosinophils in others.

The onset of the illness is marked by malaise, myalgia and arthralgia, anorexia, and loss of weight. After some months more localized symptoms appear, especially severe headache, mental confusion, and visual disturbance which may end in blindness. There may be symptoms suggesting generalized

arterial disease. A variable degree of fever is often present. The disease is self-limited, but owing to its generalized nature it may end fatally.

The etiology is unknown. It will be seen that the condition bears a close resemblance to such generalized arterial diseases as periarteritis nodosa and Buerger's disease, in both of which the inflammation may be allergic in character.

**Disseminated Lupus Erythematosus.**—In 1923 Libman and Sacks described an atypical verrucous endocarditis characterized by thrombotic non-bacterial flat vegetations resembling those of subacute bacterial endocarditis and associated with an acute type of lupus erythematosus. Gradually there has arisen a concept of a syndrome or disease characterized by a multiplicity of skin and visceral lesions, in particular some form of nephritis, the Libman-Sacks type of endocarditis (in less than half the cases), enlargement of lymph nodes and spleen, and various kinds of pneumonia. Hyperglobulinemia is a constant feature. In typical cases the initial skin lesion is a butterfly erythematous patch across the bridge of the nose which spreads rapidly. The course may be short and stormy (death in six to eight weeks), or chronic with acute exacerbations. Fever and leucopenia are common. The patient presents a toxic appearance, and frequently looks more ill than the clinical data seem to justify. The etiology is unknown, but is commonly supposed to be septic infection in a previously sensitized individual.

The lesions are widespread in many organs, and are particularly marked in the vessels, in these respects resembling periarteritis nodosa. Indeed it has been suggested that there is a relationship between the two conditions. But in disseminated lupus erythematosus the lesions are mainly degenerative rather than inflammatory, they involve the arterioles and capillaries, and they are not confined to the vascular tree. The disease is therefore quite distinct from periarteritis nodosa. Klemperer and his associates point out that the common idea that the essence of the disease is a generalized arterio-capillary thrombosis is erroneous. The basic lesion is a widespread fibrinoid degeneration of collagen, to which may be added a minor degree of reactive inflammation. (Fibrinoid degeneration is so-called because it results in the formation of a substance which resembles canalized fibrin.)

For descriptive purposes the principal lesions are cardiac, renal, vascular, and cutaneous. In the *heart* the striking gross lesion may be the flat warty vegetations of the Libman-Sacks type extending on to the mural endocardium. Microscopically the basic lesion is fibrinoid degeneration of the connective tissue of the endocardium, myocardium and pericardium. In the *kidney* the characteristic microscopic lesions are in the glomerular tufts: (1) the so-called "wire loop capillaries," (2) focal necrosis of the tuft. The wire loop appearance is due to thickening of the basement membrane of the capillaries giving a resemblance to bent wire similar to that of early amyloidosis. An appearance suggesting hyaline thrombi in the capillaries is probably due to protrusion into the lumen of the fibrinoid material in the vessel wall; true thrombosis is rare. The *vascular* lesions are most common and severe in the kidneys, but they may be present in any organ in the body. In advanced cases there may be complete fibrinoid necrosis of all the coats of the arterioles. Marked thickening of the intima may cause great narrowing of the lumen. A fulminating necrosis may call forth an inflammatory cellular reaction (lymphocytes, plasma cells, a few polymorphonuclears). In the *skin* fibrinoid degeneration occurs in the upper layer of the corium involving both collagenous fibers and ground substance. The arterioles and capillaries show the usual changes.

**Endarteritis Obliterans.**—This is not a separate entity due to a single cause, but a group of conditions in which the chief feature is a thickening of the intima with narrowing or even obliteration of the lumen. The change may be physiological, as in closure of the hypogastric vessels and the ductus arteriosus. It is seen in the involution

of old age, especially in the female reproductive organs when they have ceased to function (uterus, ovaries, breast). In organizing granulation tissue the vessels are closed by the same process. A marked degree of obliterating endarteritis is seen in the neighborhood of many chronic inflammatory foci, *e. g.*, gastric ulcer. In syphilis of the small arteries endarteritis is one of the chief features. In all of these cases the thickening is due to a proliferation of the subendothelial connective tissue.

**Ayerza's Disease.**—This is a form of endarteritis obliterans affecting the smaller branches of the pulmonary artery. The patients were called "black cardiacs" by Ayerza because of the very marked cyanosis. The chief symptoms are dyspnea, chronic cyanosis, and compensatory erythrocytosis (polycythemia). The red cells may number 10,000,000. Owing to the increased resistance in the pulmonary circulation the right side of the heart is much enlarged.

The essential lesion is a pulmonary endarteritis. The main branches of the artery are dilated and sclerosed, but the chief change is in the small arteries and arterioles. These show an endarteritis obliterans, with marked thickening of the intima and great narrowing of the lumen. Thrombosis is common. The exact cause is uncertain; indeed, it is doubtful if there is a single cause. Some cases may be syphilitic. A similar clinical picture with cyanosis and compensatory erythrocytosis may be seen in cases of extreme emphysema and in very marked fibrosis of the lungs, the result of dust irritation, but it seems better to preserve Ayerza's disease as a separate entity rather than to merge it with these other conditions, as is done by some writers.

### ARTERIOSCLEROSIS

The term arteriosclerosis is used in different senses by different writers. To the majority it is synonymous with atherosclerosis, although the standard medical dictionaries do not recognize this identity; to a few it means the diffuse sclerotic form of arterial disease; and to still others, with whom I agree, it signifies an omnibus term which includes a variety of conditions not necessarily related to one another. The inevitable result is great confusion. This is well illustrated by the fact that in the book on Arteriosclerosis edited by Cowdry, some of the contributors adopt one view, and some another. If arteriosclerosis is the same as atherosclerosis, then either one or the other term should be dropped. It seems better for the present to use arteriosclerosis in a broad sense to include a variety of non-inflammatory forms of arterial disease which may or may not have a common etiology.

Three main forms may be distinguished, which differ sharply in microscopic appearance and in some degree in distribution. These are: (1) atherosclerosis, a patchy lipoidal degeneration of the intima, by far the commonest and most important of the three; (2) medial calcification, commonly called Mönckeberg's degeneration; and (3) diffuse arteriolar sclerosis, a degenerative thickening of the intima of the smaller visceral arteries which may assume more than one form. Medial fibrosis of the medium sized arteries is common in persons over middle age. Collagenous thickening of the intima (endarteritis oblit-

erans) may cause so marked a narrowing of the lumen of the smaller arteries of the extremities in the later period of life as to lead to gangrene.

1. **Atherosclerosis.**—Atherosclerosis or atheroma is a nodular type of arteriosclerosis which affects the large arteries, especially the aorta, and the small arteries, particularly the coronaries and cerebrals. It is the fact that these arteries supply the myocardium and the brain, and that this is the only form of arteriosclerosis which commonly predisposes to thrombosis, which lends to atheroma a sinister significance. The medium-sized arteries of the muscular type are not so liable to the disease.

**Lesions.**—The *gross appearance* is most readily studied in the aorta. The most severe changes are seen in the abdominal aorta, especially in elderly persons; they are more marked in the descending than the ascending thoracic aorta. Thus the distribution of the lesions is the reverse of that seen in syphilis. They are especially marked around the mouths of the intercostal and lumbar arteries. The earliest change takes the form of yellow streaks in the intima representing deposits of fat. Such fatty streaks may be seen in young people after an attack of one of the infectious fevers. In such persons it seems probable that the lipid deposits may be absorbed and that the lesions may never progress to true atheroma, so that a distinction may be drawn between the atheromatosis of youth and the atherosclerosis of advancing years. The intima over the fatty patch becomes raised and at the same time thickened, so that the yellow color of the underlying material is no longer visible and the plaque becomes pearly and looks as if a drop of wax had fallen on the lining of the aorta. The patch contains a soft, yellow, porridge-like material from which the disease takes its



FIG. 181.—Atheroma of abdominal aorta. Thickened patches surround the openings of the lumbar arteries and there is much ulceration. (From Boyd's Surgical Pathology.)

name (*athere*, gruel). The process of atheromatous softening may reach the surface, and the pultaceous material is then discharged into the lumen of the vessel and an atheromatous ulcer is formed. (Fig. 181.) A thrombus may be formed on the surface of the ulcer which sometimes forms the starting-point of an embolus. Calcification of the lesion is very common, since lime salts are readily deposited in fatty material, and in advanced cases the wall of the aorta is converted into a calcareous tube which is cracked in places as readily as a shell. Blood may penetrate through these cracks and separate the layers of the wall. The more advanced the age of the patient, the more likely is there to be marked calcification, especially in the lower part of the abdominal aorta. To sum up, the main features are: (1) fatty streaks, (2) wax-like plaques of heaped-up intima, (3) atheromatous ulcers, and (4) calcification.

In the small arteries such as the coronaries and cerebrals the chief characteristic of the lesions is their patchiness. Yellow nodules are seen both on the outer and inner surfaces of the arteries in the circle of Willis, etc. In these small vessels the nodules may cause serious narrowing or even complete occlusion of the lumen. This, for instance, is the chief cause of gradual coronary artery occlusion. The aorta is so wide that the nodules can have no appreciable effect on its lumen.

The chief *microscopic lesion* is in the intima. There is first a deposit of lipoids, chiefly cholesterol ester, in the deepest part of the intima. Some of the connective-tissue cells may be loaded with fat. The change gradually extends from the deeper part of the intima to the surface. At the same time there is a thickening of the connective tissue of the intima overlying the fatty area, *i. e.*, the sclerotic part of the atherosclerotic process. This new tissue becomes hyaline so that no cells can be seen in it. The deeper part of the lesion consists of a kind of pulp in which the cholesterol ester is broken up into crystals of cholesterol which appear in paraffin sections as needle-like clefts. In frozen sections the lipid can be stained with Sudan and other stains for fat. Calcium salts are deposited in the fatty material and appear as fine granules stained dark blue with hematoxylin. The same change is seen in the small arteries, but here the internal elastic lamina tends to be broken up into strands, some of which pass superficial and some deep to the lesion, uniting on the far side.

It used to be thought that degenerative changes in the media were primary, and those in the intima merely secondary (Thoma). This view, for long out of fashion, is beginning again to attract attention. Blumenthal and his associates have shown by means of micro-incineration that the bluish granular material which is so familiar a feature in the media of the aorta in old persons is calcium. They found, moreover, that micro-incineration was a more sensitive indicator of calcium than staining with hematoxylin. The calcium appears to be deposited in the elastic fibers, so that calcification is proportional to loss of elasticity. Syphilitic aortitis, in which the elastic fibers are destroyed, is not associated with medial calcification. Such calcification appears



to precede the formation of atheromatous plaques in the intima, and it occurs more frequently than do the plaques.

The media may show some atrophy deep to the intimal plaque. In the aorta this is slight, but in the small vessels it may be extreme in degree, because the blood-pressure forces the intimal plaque outward producing secondary atrophy of the media.

**Effect on the Vessels.**—The elasticity of the aorta is impaired and it becomes widened, particularly in old people. At the same time it is elongated, so that it pursues a tortuous course. There is none of the extreme destruction of the media and adventitia seen in syphilis, so that aneurism is a rare sequel, but it may occur. In the small vessels there may be great narrowing of the lumen (Fig. 182) with softening



FIG. 182.—Atheroma of a cerebral vessel. The thickened intima shows degeneration in its deeper layers, and there is some atrophy of the media underlying the thickened plaque.  $\times 125$ .

of the brain and necrosis and scarring of the myocardium. An atheromatous patch on a cerebral vessel is a source of weakness, and is a very common cause of cerebral hemorrhage, and also of cerebral thrombosis. It may lead to the formation of a small aneurism owing to involvement of the internal elastic lamina by the atheromatous process.

**Etiology.**—The etiology of atherosclerosis is of prime importance if anything is to be done to prevent this common disability of declining years, but in spite of a vast amount of work the problem remains unsolved. The essential lesion is the accumulation of lipoid, mainly cholesterol and its esters, in the intima. As to the significance of this accumulation there are two views: (1) that intimal degeneration is primary and deposition of lipoids secondary; (2) that lipoids are first

deposited, the degeneration being secondary. The available evidence seems to support the former view.

From the work of Bloor and others it would appear that cholesterol is concerned with the transport of fatty acids to the cells for utilization. It is probable that the union of cholesterol and fatty acids (esterification) occurs in the intestine, that transport to the tissues takes place in the form of ester, and that in the tissues the fatty acid is split from the cholesterol (hydrolysis) by means of an enzyme system (esterase). The fatty acid is then utilized by the cells and the cholesterol is removed. Theoretically this mechanism might be upset in two ways: (1) if cholesterol esters are present in too great amount in the blood, the enzyme system may be inadequate so that lipid accumulates in the tissues; (2) if the enzyme system itself breaks down, similar lipid accumulation may occur.

Aschoff revived Virchow's original conception that atheroma is due to an imbibition of plasma by damaged intima with consequent deposition of lipid in the ground substance. It is probable that under normal conditions plasma is continually passing into the intima either through the endothelium or by way of fine vascular channels. In some cases overloading of the intima with lipoids is probably due to hyperlipemia, as in the atheroma which so frequently complicates diabetes even in young persons. Anitschkow produced atheromatous deposits in the aorta of rabbits by feeding them a diet high in cholesterol. Leary succeeded in reproducing with remarkable exactness the lesions of human atherosclerosis in the coronary arteries of rabbits by feeding them with cholesterol for long periods. Duff points out in an able critical review that the results of cholesterol feeding in rabbits afford no grounds for the belief that human atherosclerosis is related to high cholesterol in the diet or to hypercholesterolemia. The normal blood cholesterol of the rabbit is low and is markedly raised by the administration of cholesterol, whereas in man the normal level is high. The effect on the intima will therefore be very different in the two cases. Experimental cholesterol atheroma cannot be produced in dogs and cats, so that there exists a sharp species difference in experimental animals. This may be due in part to the fact that the herbivorous rabbit is unable to metabolize cholesterol, whereas the omnivorous cat and dog possess this capacity. It is also possible, as suggested by McArthur, that the species difference lies in the capacity of the enzyme system in the arterial wall. If this system is inadequate to deal with the lipoids presented to it, the latter cannot fail to accumulate in the intima.

In the vast majority of cases of human atheroma there is no evidence of hypercholesterolemia, although diabetes, nephrosis, etc., offer exceptions to this rule. Although some workers believe that a high cholesterol content in the diet is the essential etiological factor (Leary and others), it appears more probable that the fault lies within the arterial wall. In this respect atheroma is analogous to cholesterosis of the gall bladder.

Various factors may be responsible for interference with the ester-splitting mechanism. Of these factors age, heredity and strain, particularly hypertension, deserve consideration. (1) Atherosclerosis is a degenerative process associated with advancing years which in one way seems as natural as the graying of the hair. It is the end of a song that is sung in the cradle. As Clifford Allbutt remarks: "It cannot be supposed that the stealthy hours carry away no qualities of tissue, no quantities of energy." The older the person the more likely is there to be marked atheroma. But in persons over eighty years of age the aorta may show hardly a trace of atheroma, whereas it may be present in the young. It is possible that it is the elastic fibers of the media which are damaged by the ageing process, and that the loss of elasticity may lead to degeneration of the intima. The fine vessels supplying the deeper layer of the intima have no muscular coat, and are dependent on the contractility of the aorta for a continuous flow of blood through their channels. (2) Heredity certainly plays a part. Mortensen, in an analysis of 300 cases of atherosclerosis, found a family history in 67.5 per cent, and many of the remainder did not know the cause of death of their ancestors. O'Hare obtained a positive family history in 68 per cent of cases. One patient, whose father died of apoplexy and mother of cardiovascular-renal disease, had 9 brothers and sisters all of whom had died of apoplexy, and he himself had already had a stroke. (3) Hypertension is a difficult factor to assess, because it is common in the same age period as atheroma, and the association may be incidental rather than causal. Moreover, different sites must be considered separately. No accurate statistical data are available, but the following generalization appears justifiable: no causal connection in atheroma of the aorta, frequently connection in coronary atheroma, probable connection in cerebral atheroma. Goldblatt has never seen atheroma of the aorta in hypertensive dogs. It must be admitted that a number of facts, mostly related to local strain, may be cited against the above statement. In coarctation of the aorta in young people there may be marked atheroma above the point of narrowing, and lesser degrees are common in the pulmonary artery in mitral stenosis. Prolonged experimental hypertension in the rabbit (an unsatisfactory animal for atheroma experiments) leads to the formation of atheromatous plaques in the aorta (Dill and Isenhour). In these cases there is no elevation of the blood cholesterol. Aortic lesions are nearly always most pronounced at points which may be considered specially subject to strain, such as the bifurcation of the aorta and the sites of origin of the intercostal and lumbar arteries. Winternitz believes that atheroma is closely associated with interference with the blood supply of subintimal areas by injury to the vasa vasorum which enter this region. Syphilitic aortitis is frequently accompanied by atheroma, but the latter condition is much more marked in the wall of an aneurism. The stretching of the wall seems to cause tissue damage which allows accumulation of lipoids in the intima. Wilens found that the application of cylindrical silver cuffs to the femoral

and carotid arteries of rabbits, followed by cholesterol feeding, led to localization of lipoids in the intima at the points of pressure.

The esterase mechanism may be under chemical or hormonal control. This is suggested by the fact that the cholesterolemia of the aorta produced in rabbits by feeding cholesterol is prevented by the administration not only of thyroid gland, but also of iodine. It is said that thyroidectomy causes marked increase in the blood cholesterol, and it is well known that the level is high in myxedema. The incidence of atheroma in Iceland is remarkably low (Dungal), and it has been suggested that this may be due to the abundant iodine supply in the food, soil and air of that country. Atheroma is also very uncommon in China, as are other conditions involving disturbance of lipid metabolism. The facts of geographic pathology are always of interest, but fact must be distinguished from theory, and it is wise not to let fancy run too free in suggesting explanations. Possibly the temporary lipid deposits in the intima which are met with in adolescence may be due to transient inhibition of esterase due to hormonal imbalance.

The deposited cholesterol and cholesterol ester are taken up by phagocytes, which become pale, swollen, vacuolated "lipoid cells." Cholesterol, like silica, may remain as an inert substance in the tissues and act as a chronic stimulant to fibroblasts with consequent fibrosis. Leary has shown that cirrhosis of the liver develops in the rabbit as the result of feeding with cholesterol. It is highly probable, therefore, that deposition of lipid in a damaged intima represents the primary factor in the production of atherosclerosis, the sclerosis being a secondary phenomenon.

In the discussion of coronary atherosclerosis reference has already been made to Duguid's suggestion that some of the lesions may represent organization of a thrombus which becomes incorporated with the intima with subsequent fatty degeneration (page 373). This is a revival of a theory advanced by Rokitsansky nearly one hundred years ago.

Further discussion of the etiology of atheroma will be found in the papers of Page, Duff, and Leary.

**2. Medial Sclerosis of Mönckeberg.**—This is the type of arteriosclerosis which is observed by the clinician when he feels the arteries, for it is the vessels of the limbs, arteries of the muscular type, which are affected. The pipe-stem radials, the tortuous and prominent temporals, belong to this class. The condition is a senile degenerative change with no relation to high blood-pressure, although the long-continued administration of adrenalin in animals leads to calcification of the media. In these respects it resembles atheroma. The two lesions may both be present in the same artery. What relation, if any, it bears to atheroma it is not safe at present to say. The arteries most affected are the femoral, popliteal, the radial just above the wrist, and the parietal vessels such as the gluteal and pudendal. The visceral arteries (mesenteric, etc.) are seldom involved, but typical examples may be seen in the uterus and ovary in old persons.

**Lesions.**—It is probable that the first change is fatty degeneration of the media. Calcium is then deposited in the degenerated tissue, and the vessel becomes hard and brittle.

The chief *microscopic* change is in the media. (Fig 183.) The muscle fibers undergo fatty changes with degeneration, fragmentation, and the deposition of lime salt. These may be in the form of fine granules or large masses. Bone containing bone-marrow has sometimes been observed. The other coats are often normal, in which case there will be no narrowing of the lumen. Atheroma is often added, and this may produce marked occlusion, a change seen in senile and diabetic gangrene of the leg.



FIG. 183.—Monckeberg's sclerosis of ovarian vessels. In the media of three of the arteries there is a large deposit and in the fourth a small deposit of lime salts.  $\times 16$ .

**Medionecrosis of the Aorta.**—With advancing years the aorta often develops a basophilic mucin-like substance in the interstitial tissue of the media which stains blue with hematoxylin and red with thionin and polychrome methylene blue, so that it has been called the chromatropic substance. (Fig. 184.) This substance may replace the lamellar of elastic and muscular tissue to a considerable extent, and focal necrosis may develop in these areas of chromatropic or mucinous degeneration, especially in the inner and middle thirds of the wall. Cyst formation may occur in these necrotic patches, the idiopathic cystic medionecrosis of the aorta first described by Erdheim. The importance of the condition lies in the fact that it is the chief lesion found in the rare cases of spontaneous rupture of the aorta, and it probably plays a part in the development of dissecting aneurism of the aorta.

**3. Diffuse Arteriolar Sclerosis.**—This form of arterial degeneration is also called arteriolosclerosis and diffuse hyperplastic sclerosis. The term arteriole is vague and not susceptible of strict definition. In the present connection it is used to indicate the smaller arteries of the viscera, the intimate vasculature, vessels 100 microns in diameter or

less. The lesions are not all of one type, but in general they cause thickening of the wall and narrowing of the lumen. Arteriolar sclerosis may be widespread, but is most frequent in the spleen, pancreas, kidney and adrenal. The arteries involved are of a smaller order than the "small" arteries affected by atheroma, *e. g.*, coronary and cerebral vessels.

Hypertension and the aging process seem to be the two principal etiological factors. That hypertension is a causal agent is indicated by the fact that identical lesions are found in the experimental hypertensive animal. On the other hand similar lesions, although usually less pronounced, may be present in persons without hypertension, especially in the aged. Hypertension appears to accentuate and speed up a normal wear-and-tear degenerative process.

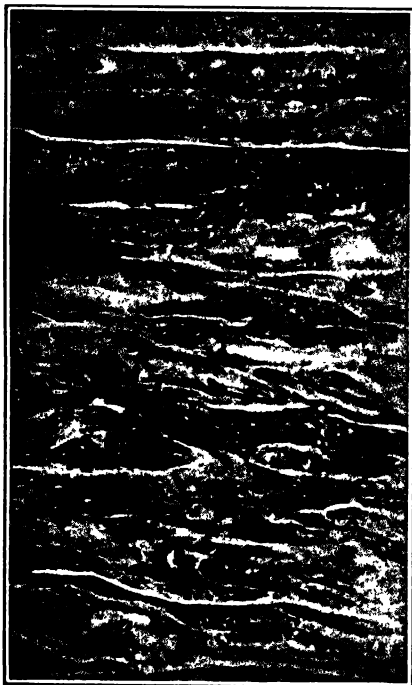


FIG. 184.—Medionecrosis of aorta, showing chromatropic substance.  $\times 400$ .

It is in hypertension that the lesions are best developed. Essential hypertension, which constitutes 90 per cent of all cases of hypertension, may be divided into so-called benign and malignant forms. The benign form is characterized by a gradual onset and a long-continued course often of many years. The malignant form, very much less common, is frequently of abrupt onset and runs a course measured in months rather than years. It often ends with renal failure (uremia), but not necessarily so. The lesions of hypertensive arteriolosclerosis differ in the two forms, although the distinction between the two

is not always as sharp as indicated here. In each form there may be two significant lesions.

**Benign Form.**—The characteristic lesions are hyaline degeneration and elastic hyperplasia. *Hyaline degeneration*, the commonest manifestation of arteriolosclerosis, is best seen in the smallest vessels, such as the afferent arterioles of the kidney, although not confined to these vessels. There is a sharply defined, smooth, acidophilic thickening of the subintimal tissue. In course of time the change may involve the entire thickness of the wall (Fig. 185), but some trace of nuclear structure usually remains. The appearance suggests an accumulation or deposition of hyaline material which leads to narrowing and in extreme

cases to complete obliteration of the lumen. In the spleen hyaline arteriosclerosis is so common as to have no pathological significance. In the kidney it is almost invariably associated with hypertension, whereas in non-hypertensives the kidney is one of the organs least frequently involved. In no other organ is there this constant relationship between arteriosclerosis and hypertension, but in such organs the lesions are more frequent and more severe in persons with hypertension. Hypertension is, therefore, the most important causal factor, but, except in the case of the kidney, it is not an essential factor.

*Elastic hyperplasia*, sometimes called elastosis, is most marked in the larger arterioles and medium-sized arteries, but some degree of it can be seen even in the smallest vessels. The internal elastic lamina is split up into several layers, a process known as reduplication. (Fig. 186.) There may also be proliferation of endothelial cells which become intermingled with the new elastic fibers. At first the elastosis is confined to the intima, causing narrowing of the lumen, but as time goes on both intima and media are seen to be composed largely of elastic fibers in sections stained to show that tissue. The muscular type of artery has become converted into the elastic type characteristic of large arteries such as the aorta which are designed to withstand great strain and are little more than passive conducting tubes. The amount of elastic tissue in the walls of an artery approximately corresponds to the pressure of blood within it.

**Malignant Form.**—In the malignant form of hypertension, in which the process has a quickened *tempo* and the vessels have less time to adapt themselves to increased strain, the characteristic lesions in their order of importance are arteriolar necrosis and cellular hyperplasia. In *arteriolar necrosis*, also called necrotizing arteriolitis, the whole thickness of the vessel wall becomes necrotic and structureless. (Fig. 187.) The affected area stains diffusely red with eosin, and its limits are fuzzy and indistinct, as if it had been freshly painted and someone had smeared it with his thumb. This is in sharp contrast to the clean-cut smooth appearance of hyaline degeneration, in which sharply defined nuclei often persist. A rapid rise in blood-pressure is likely to lead to arteriolonecrosis due to the sudden and severe mechanical strain and extreme vasoconstriction. The lesion can be produced in the course of a few days in the experimental animal. The necrotic wall often becomes infiltrated with red cells, and hemorrhage is common, especially in the brain. Aneurismal dilatation can occur. Arteriolonecrosis is commonly seen in hypertension complicated by renal failure (uremia), and it is possible that toxic products in the blood may play a part in its production. *Cellular hyperplasia* commonly called productive endarteritis and hyperplastic arteriosclerosis, is a condition in which the walls of the arterioles are thickened by a concentric cellular proliferation, so that they may present an "onion-skin" appearance. (Fig. 188.) The proliferation may be mainly subintimal, so as to merit the term endarteritis, but often the hyperplasia is most marked in the media, a natural response to the increased intravascular pressure.

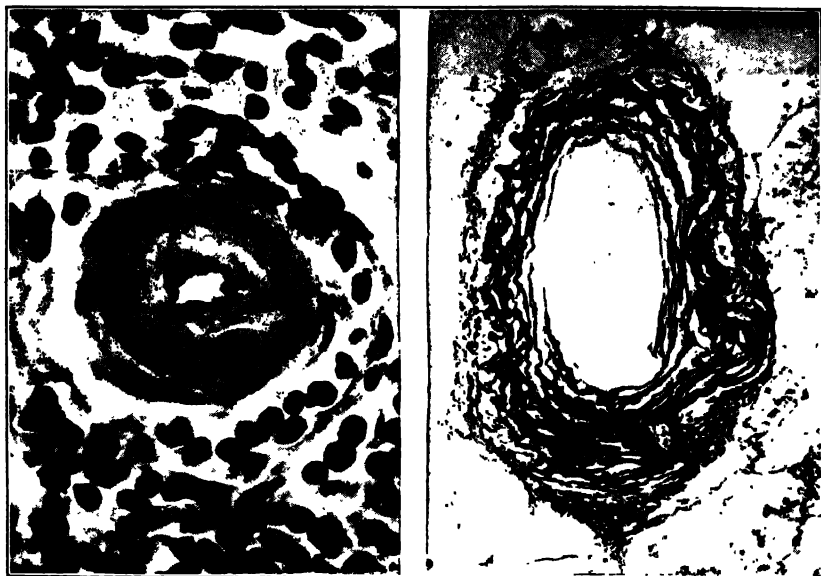
**Benign**

FIG. 185.—Hyaline degeneration.  
× 510.

FIG. 186.—Elastic hyperplasia.  
× 500.

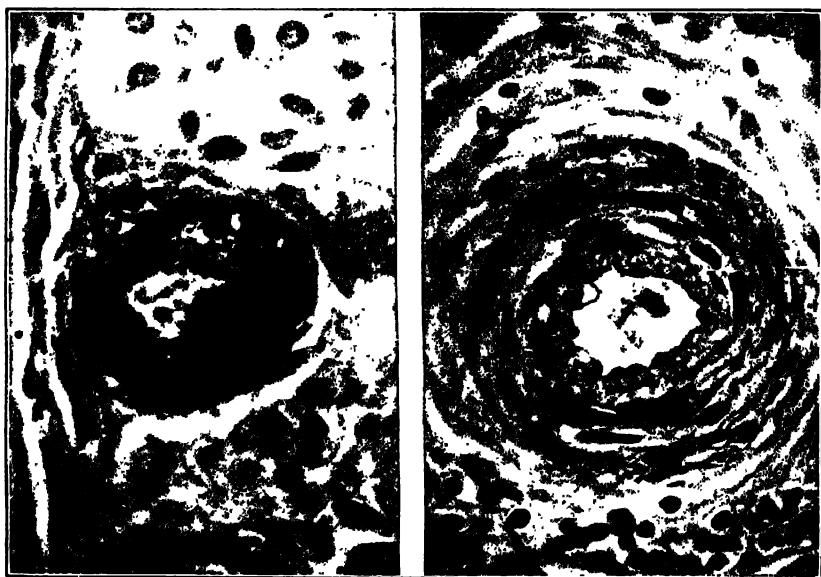
**Malignant**

FIG. 187.—Arteriolar necrosis.  
× 430.

FIG. 188.—Cellular hyperplasia.  
× 340.

FIGS. 185, 186, 187, 188.—ARTERIAL CHANGES IN HYPERTENSION.



Without an elastic tissue stain it may be impossible to distinguish the limits of the nucleated thickened intima and the hyperplastic media. When the process is slower the nucleated appearance is lost and the new tissue becomes collagenous. Fatty degeneration may be marked in frozen sections. Elastic hyperplasia of the intima is not a special feature of the condition; such hyperplasia appears to be a reaction to gradually increasing and prolonged hypertension. It may, of course, be present in the medium-sized arteries of any one over middle age, but under these conditions it has no significance.

For the sake of convenience these four lesions have been described separately. They may, however, be combined and intermingled, for the slow (benign) form may have an acute (malignant) termination. Similar arteriolar lesions are seen in the hypertension of glomerulonephritis.

### ANEURISMS

An aneurism is a localized dilatation of an artery.

**Causes.**—Every aneurism is caused by weakening of the arterial wall. As a rule, it is the media which is damaged. Syphilis is by far the most important cause of aneurism of the large arteries, but extensive atheroma may be responsible for aneurism of the aorta in elderly persons. Syphilis seldom or never leads to aneurism formation in the small arteries, because in them the lesion is a diffuse thickening of the intima with little involvement of the media. An infected embolus will lead to suppuration of the vessel wall and destruction of the media so that an infective or *mycotic aneurism* is formed. Periarteritis nodosa may weaken the vessel from the outside and lead to the formation of multiple small aneurisms. Infection from an abscess or a tuberculous focus may form the starting-point of an aneurism. Finally, congenital weakness of the media in the arteries at the base of the brain has been suggested as a cause of a *congenital aneurism*.

**Varieties.**—A *true aneurism* is one in which the sac is formed by the wall of the vessel.

A *false aneurism* is one in which the sac is formed by the surrounding tissues. It is caused by the rupture of a vessel, and is a hematoma rather than an aneurism.

A *fusiform aneurism* is a dilatation of a segment of the vessel, and is seen in the aorta and its large branches.

A *saccular aneurism* is a pouching of the vessel at one point. This is the usual form of aneurism.

A *traumatic aneurism* is a false aneurism, a hematoma, formed by laceration of the vessel wall.

An *arteriovenous aneurism* is an abnormal communication between an artery and a vein, usually due to simultaneous laceration of an adjoining artery and vein. It was common during the World War. The blood passes from the artery into the vein, and produces a local distention of the vein which pulsates as forcibly as the artery.

A *congenital arteriovenous fistula* is a direct "shunt" between an artery and a vein without the interposition of capillaries. The blood passes forcibly into the vein, which becomes dilated (arteriovenous varix). The lesion is commonest in the leg, but may occur in the arm or the scalp; in the latter position, it forms a mass of dilated vessels known as a *cirsoid aneurism*. The clinical features are striking and make recognition easy: (1) higher blood-pressure and temperature in the affected limb; (2) increased circumference of the limb and the presence of bruits and thrills; (3) cardiac hypertrophy; (4)



FIG. 189.—Dissecting aneurism of the aorta. The media of the ascending aorta has been split into two layers. The dark mass between the layers is blood.

venous blood is redder on the affected side (pathognomonic); (5) roentgen-ray visualization of the fistula after the injection of thorotrast (arteriography).

A *dissecting aneurism* is not a true aneurism, *i. e.*, the vessel is not dilated. A hemorrhage occurs in the media of the aorta between the middle and outer thirds, commencing at the base and spreading along the vessel for a variable distance, splitting the media into two layers in its passage. (Fig. 189.) The blood tends to encircle the aorta, and may pass along its entire length to the bifurcation. In one of my cases the blood had dissected its way along the renal, splenic and superior mesenteric arteries causing gangrene of the bowel through pressure on the latter vessel. There may be ischemic necrosis of various tissues due to the blood in the wall of the aorta compressing the exit of arterial branches, as for instance, in the case of the spinal arteries. On this account there may be a confusing multiplicity of symptoms.

Usually the blood ruptures externally, with death to the patient, but it may rupture into the lumen. Should the patient survive, the blood may be absorbed, and two tubes are formed, one inside the other. Dissecting aneurism is a disease of later life, and is rare before the age of fifty years. The primary lesion in the great majority of cases is marked medionecrosis of the aorta causing rupture of the vasa vasorum, but I have seen an occasional instance of blood entering the media through an atheromatous crack in the intima. As a rule a tear in the intima (especially at the spot where the latter is normal) is an effect

rather than a cause of the condition. Syphilis is not a factor of any importance. There may be large collections of lymphocytes and plasma cells in the adventitia; this is not the result of syphilis, but is due, apparently, to irritation produced by the accumulation of red blood cells in the wall of the aorta. The blood-pressure is usually high unless the patient is *in extremis*, and the heart is correspondingly enlarged. The *symptoms* are characteristic. The patient is seized by a sudden sharp pain in the chest, accompanied by prostration. He often experiences what he described as a tearing sensation. The pain passes off, but in a typical case death occurs some days later from the bursting of the aneurism into the pericardial sac, the chest, or the abdominal cavity.



FIG. 190.—Edge of aneurism of aorta. Showing how the elastic tissue (black) suddenly ceases. Elastic tissue stain.  $\times 75$ .

**Aneurism of the Aorta.**—Aortic aneurism is so infinitely more common and more important than the other forms that it will be considered separately. This type of aneurism is caused by syphilitic mesaortitis with destruction of the elastic tissue. (Fig. 190.) Each time the aorta dilates it does not quite return to the normal size owing to destruction of the elastic tissue. As the destruction is more marked in one place than another, a bulging occurs in the weakened area. Heavy manual labor with periodic strain, lifting heavy weights, etc., will hasten the development of the condition. Atheroma may weaken the aorta sufficiently to lead to the formation of an aneurism; this is most likely to be a fusiform aneurism of the abdominal aorta.

The dilatation begins in the ascending aorta or the arch. (Fig. 191.) Usually it is localized (saccular aneurism), but sometimes it is more

uniform (diffuse aneurism). The mouth has a smooth rolled edge. The aneurism may grow forward, eroding the sternum, or backward, eroding the bodies of the vertebræ (though not the intervertebral disks), causing great pain in the back. It may press on the trachea with difficulty in breathing, on the esophagus with difficulty in swallowing, on the left recurrent laryngeal nerve with hoarseness and aphonia. It may rupture on the surface, or into the trachea, bronchi, esophagus, pericardium, or pleural cavity.



FIG. 191.—Aortic aneurism. The rolled edge is well seen, as well as the characteristic nodular appearance of syphilitic aortitis. The aortic cusps are normal.

The adjoining parts of the aorta show the characteristic wrinkling of syphilitic aortitis, but in the aneurismal sac the direct evidence of syphilis is usually obscured by atheroma. Thrombosis occurs on the roughened lining, and layer after layer of clot is laid down and becomes incorporated with the wall of the sac. The clot therefore shows a characteristically laminated appearance. Microscopic examination of the wall of the sac shows that it consists only of adventitia; the intima

and media have disappeared. Adjoining parts of the wall show the microscopic lesions of active syphilitic aortitis.

**Angiospastic Diseases.**—The muscular walls of the arterioles are supplied both with constrictor and dilator fibers. In inflammatory conditions of arteries such as Buerger's disease the lesion irritates the sensory sympathetic fibers and thus causes constriction of the anastomotic and terminal arteries. For this reason operative procedures designed to paralyze the sympathetic may be of great benefit by increasing the collateral circulation. Recent embolism and rapid thrombosis have a similar action on the sympathetic. In advanced non-inflammatory arterial occlusion (arteriosclerotic) there is inhibition of vasoconstrictor tonus, so that no benefit is obtained by paralyzing the sympathetic. *Raynaud's disease* is a condition of long-continued arterial spasm resulting in local asphyxia and symmetrical gangrene. It usually affects the fingers. It is generally believed that the essential cause is a disturbance of the vasomotor mechanism, although it has been suggested that there is some local fault in the periphery independent of the vasomotor mechanism (Lewis). Mild cases of angiospasm ("dead fingers") are very common; they occur almost exclusively in women. Vasodilatation is the basis of *erythromelalgia* (*erythros*, red; *melos*, limb; *algos*, pain), a condition marked by a paroxysmal throbbing and burning pain usually in the feet, sometimes in the hands, accompanied by a dusky mottled redness of the parts.

## THE VEINS

### PHLEBITIS

Inflammation of a vein or phlebitis differs from inflammation of an artery in the greater tendency to thrombosis and the correspondingly lessened tendency to hemorrhage. The inflammation may be suppurative or non-suppurative.

**Suppurative Phlebitis.**—The inflammation is caused by pyogenic bacteria which usually invade the vein from without. A vein passing through an abscess or an area of cellulitis is much more likely to become inflamed and thrombosed than is the corresponding artery. The entire thickness of the wall is invaded by leucocytes and thrombosis rapidly occurs, so that the condition may be called a thrombophlebitis. The thrombus becomes septic, softens, and is likely to disintegrate with the formation of emboli. Hemorrhage is not common, because the thrombosis advances ahead of the inflammation and closes the vessel. Some of the most important examples of suppurative thrombophlebitis are as follows: phlebitis of the lateral sinus following acute otitis media and threatening to extend down the jugular vein; phlebitis of the facial veins following a boil or carbuncle of the nose or upper lip extending through the ophthalmic veins to the cavernous sinus; phlebitis of varicose hemorrhoidal veins (piles); phlebitis extending from the appendix to the portal vein and causing a portal pyemia; phlebitis of the pelvic and femoral veins following puerperal sepsis or operations on the female pelvic organs; phlebitis of varicose veins of the leg when ulceration has occurred. In all of these instances the great danger is that multiple septic embolism may occur and a condition of pyemia be set up.

**Non-suppurative Phlebitis.**—When a vein is ligatured an aseptic phlebitis occurs accompanied by thrombosis. Owing to the absence of infection the thrombus is invaded by capillaries and fibroblasts and organized into fibrous tissue. The presence of a thrombus is of itself sufficient to produce an inflammatory reaction in the vein wall. This is apt to be mistaken for a primary inflammation, and the condition is wrongly labelled thrombophlebitis.

**Primary Idiopathic Thrombophlebitis.**—This peculiar condition is a primary disease in otherwise normal persons. In most cases it is a *thrombophlebitis migrans*, now one, now another short segment of vein being involved, often in recurring attacks. Occurring for the most part in young and middle-aged men, it appears to be an inflammatory disease of small and medium-sized veins, and may be regarded as a type of thrombo-angiitis obliterans which involves only the veins.

### PHLEBOSCLEROSIS

The condition of phleboscrosis or phlebofibrosis is not uncommon, although seldom recognized because seldom looked for. It does not appear to be related to arteriosclerosis, for it occurs at an earlier period of life, being commonest in young men between twenty and thirty years of age; it is not associated with fatty degeneration or calcification; and it bears no relation to hypertension. It affects chiefly the veins of the legs, where the affected vessels feel like hard mobile cords, which may be mistaken for tendons. There are no associated symptoms. It is a disseminated lesion affecting both superficial and deep veins and is always bilateral. It has been called endophlebitis and hyperplastic phlebitis, but it is a degenerative and not an inflammatory condition. The affected vein is thickened and the lumen narrowed. The chief microscopic change is a marked increase of the connective tissue of the media and corresponding atrophy of the muscle fibers, together with a lesser fibrosis of the intima. The innermost layers of the thickened intima are hyaline, and the endothelial lining is missing. The distinction between the coats of the vessel is largely lost. The exact nature of the condition is uncertain and the cause is quite unknown.

### VARICOSE VEINS

A varix or varicose vein is one that is dilated, lengthened, and tortuous. The three common sites are: (1) The veins of the leg, especially the internal saphenous; (2) the hemorrhoidal veins (hemorrhoids or piles); (3) the pampiniform plexus of the spermatic cord (varicocele).

**Causes.**—These may be predisposing and exciting. An important *predisposing* cause appears to be a congenital and inherited weakness of the walls and valves of the veins. The condition may run in a family for generations, and the same vein may be affected each time. The *exciting* factor is an increase of pressure in the vein, and may be caused in the following ways: (1) Central obstruction to the venous return (mitral stenosis, emphysema, cirrhosis of the liver). (2) Pressure of a tumor, gravid uterus, or loaded rectum. (3) Prolonged standing. (4) Straining and violent muscular efforts. The former aggravates piles, while the latter explains the frequency of varicose veins of the legs in athletes.

**Lesions.**—The valves give way, and the vein becomes dilated, elongated and tortuous. A phleboscrosis develops. At first there is

hypertrophy of the media from increased strain, followed later by atrophy and replacement fibrosis. The intima and adventitia also become fibrosed and thickened. The thickening is irregular, and pouching of the wall occurs in the intervals. Thrombosis in these pouches is very common.

**Effects.**—The effects are felt by the veins and the tissues which they drain. Hemorrhage, phlebitis, and thrombosis are the important venous complications. Hemorrhage is commonest in the case of piles, where the veins are covered only by mucous membrane (hence the name hemorrhoids). There may be hemorrhage from the veins of the leg as the result of trauma or ulceration of the overlying tissue. The hemorrhage may be into the tissue or on the surface. The presence of ulceration naturally predisposes to infection and thrombosis.

The *tissues* suffer severely as the result of the varicosity. There is chronic congestion and the circulation is greatly interfered with. Edema is apt to develop, probably as the result of an associated lymphangitis, the overlying skin becomes sodden and devitalized and atrophic from pressure, and a varicose ulcer may be formed, usually on the lower third of the leg. This type of ulcer is likely to be very chronic, and may heal and break down repeatedly, causing great disability and suffering to the patient. The skin of the lower part of the leg acquires a mahogany-brown color, due to pigmentation from repeated small hemorrhages into the tissues. The modern treatment of varicose veins and varicose ulcers has completely changed the previously rather gloomy outlook.

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## CHAPTER XVII

### THE RESPIRATORY SYSTEM

#### THE NOSE

**Granulomata.**—Many granulomatous infections may involve the nose, but the only common one is syphilis. They all show a formation of new tissue, followed by necrosis, ulceration, and destruction of the septum.

**Syphilis.**—Syphilis of the nose is common. It may be congenital or acquired. The *congenital* form may cause an atrophic rhinitis with foul-smelling discharge. Or it may destroy the septum, cartilage, and bone so that the bridge falls in, giving the *saddle nose* so characteristic of congenital syphilis. The *acquired* tertiary lesion is a gumma which perforates the septum and may destroy the bridge of the nose so as to give the more uncommon “saddle nose” of acquired syphilis.

**Tuberculosis.**—Tuberculosis of the nose is rare, and is usually a complication of pulmonary tuberculosis. It is likely to produce an ulcerative lesion of the cartilaginous part of the septum.

**Leprosy.**—Leprosy starts as a nodule which enlarges, undergoes ulceration, and may cause perforation of the septum.

**Rhinoscleroma.**—Rhinoscleroma is a disease of inhabitants of Eastern Europe. As the name implies, the lesion of the nose is peculiarly hard. The condition commences in the nose, but tends to spread to the pharynx. It is at first proliferative and then destructive. The characteristic Mikulicz cells and other microscopic features are described in Chapter VII.

**Glanders.**—Glanders is a very rare infection of the nose in man, although common in the horse. As usual, there is proliferation followed by destruction. The glanders bacilli are present in the secretion. The bacteriology and pathological lesions are given in Chapter VII.

**Tumors.**—Tumors of the nasal cavity are usually polypoid in type. The commonest form of nasal polyp is not really a tumor, but an edematous mass of inflamed and hypertrophied mucous membrane. It is usually attached to the lateral wall near the opening of the antrum of Highmore, and hangs down as a soft mucoid globular mass with a well-defined pedicle. Sometimes a proliferation of mucous glands may suggest an adenoma. Carcinoma is uncommon and sarcoma still more rare.

#### THE LARYNX

##### LARYNGITIS

Infections of the nasopharynx will readily spread down and infections of the bronchi spread up to the larynx. We may recognize the following forms of laryngitis: simple, diphtheritic, tuberculous, and syphilitic.

**Simple Laryngitis.**—The inflammation is usually *acute*. It may form part of a common cold or may occur in the course of one of the infectious fevers, especially measles and scarlet fever. Pneumococci, streptococci, and *Micrococcus catarrhalis* are the commonest organisms. Non-bacterial irritants such as steam and chlorine gas may cause violent inflammation. The lesions are those of acute inflammation of any mucous membrane. The membrane is swollen and congested and is covered by mucus poured out by the glands. Microscopically it is infiltrated with inflammatory cells.

*Chronic* laryngitis may be caused by excessive smoking, chronic alcoholism, or undue use of the vocal cords. The surface of the mucous membrane is dry and covered by small papillary projections. The epithelium is thickened and opaque (pachydermia). The submucosa is infiltrated with chronic inflammatory cells. In typhoid fever there may be swelling of the lymphoid tissue of the larynx, and in rare cases ulceration of the cartilage.

**Diphtheritic Laryngitis.**—Diphtheria is primarily a disease of the pharynx, but the infection frequently spreads to the larynx. A “false membrane” consisting of fibrin, leucocytes, and necrotic epithelial cells is formed on the surface, but is firmly attached to the underlying tissue. A membranous type of laryngitis may also occur in streptococcal and other severe infections.

**Tuberculous Laryngitis.**—This is practically always secondary to pulmonary tuberculosis. It is fortunately not nearly as common as might be expected. Tubercles are formed in the subepithelial tissue. These undergo necrosis, and shallow lenticular ulcers are formed on the surface. The disease begins in the arytenoid region or the vocal cords, and may spread extensively so as to involve all other parts of the larynx. Eventually there may be widespread destruction of the cartilages and the epiglottis, a peculiarly distressing condition because food tends to pass down into the trachea and lungs.

*Lupus* is a rare and much less serious form of tuberculosis of the larynx. It is secondary to lupus of the face or nasopharynx. Small nodules are formed with superficial ulceration, but there is none of the extensive destruction characteristic of tuberculous laryngitis.

**Syphilitic Laryngitis.**—In the secondary stage there may be catarrh or mucous patches. In the tertiary stage there is destruction followed by healing and scar formation. Papillary masses of new tissue may be formed. The scarring leads to distortion of the larynx, stenosis of the glottis, and a characteristic hoarseness of the voice.

### EDEMA OF THE GLOTTIS

Edema of the glottis occurs in the course of an acute inflammation such as diphtheria or that caused by the inhalation of steam, irritating gases, etc. It may be part of an angioneurotic edema, but seldom forms part of a general cardiac or renal edema. There is great swelling of the loose tissue in the posterior wall of the pharynx, the false vocal

cords, etc. The parts are very swollen and boggy. The edema may develop acutely and may cause death from suffocation.

### TUMORS OF THE LARYNX

**Papilloma.**—This is the commonest tumor of the larynx. It is a small warty growth composed of loose connective tissue, and usually arises from the vocal cords or the anterior commissure. It is common in singers and others who have to use the voice much. The tumor behaves differently in adults and children. In the adult it shows a strong tendency to recur after removal, and occasionally, though rarely, becomes malignant. In the child there is also a strong tendency to recur, no matter how radical the removal, but the new tumors are often at other sites in the larynx, and in time there is most likely to be spontaneous cure. In children, therefore, multiple recurrent papilloma is a benign self-limited disease.

**Nodular Fibroma.**—This is not uncommon in children. It is a small sessile growth composed of vascular connective tissue.

**Carcinoma.**—Cancer of the larynx is far commoner in males than in females, and often shows a definite relation to chronic irritation, such as overuse of the voice or abuse of tobacco and alcohol. Two forms may be recognized, intrinsic and extrinsic. The *intrinsic* form constitutes 80 per cent of the cases, and arises from the vocal cords, usually the anterior third. The tumor, originating from fully differentiated stratified squamous epithelium, often remains confined to the larynx for a considerable time, and offers a good chance of recovery after operative removal as well as being quite radiosensitive. The *extrinsic* form arises in the pyriform fossa, the aryepiglottic folds, or on the epiglottis itself. It involves the hypopharynx, invades the surrounding tissue, and gives rise to early lymph node metastases. This is one form of hypopharyngeal carcinoma. Carcinoma of the larynx begins as a small indurated patch or as a papillary tumor. In the later stages there is extensive destruction, ulceration, and sepsis with the danger of lung abscess or inhalation pneumonia. The intrinsic form is epidermoid, the extrinsic form usually transitional in type.

**Sarcoma.**—A rare tumor.

## THE BRONCHI

### BRONCHITIS

**Acute Tracheobronchitis.**—Acute inflammation of the bronchi affects either the large bronchi and trachea or the small bronchioles. The latter condition is associated with pneumonia, while the former occurs in a pure form which may be called tracheobronchitis.

**Etiology.**—The irritant may be bacterial, mechanical, or toxic. The bacteriology of acute bronchitis is by no means certain, but it is

probable that the pneumococcus, micrococcus catarrhalis, streptococcus, staphylococcus, and influenza bacillus may at different times be responsible. Their presence in the sputum does not prove that they have caused the inflammation in the bronchial wall. Acute bronchitis may complicate any of the infectious fevers, especially the early stages of typhoid. Dust, steam, poisonous gases, and ether may all produce acute tracheobronchitis.

**Lesions.**—The mucous membrane of the trachea and large bronchi is red, swollen, and covered with a tenacious exudate which may be mucoid or purulent. Microscopically the mucosa is greatly congested and infiltrated with leucocytes. It is remarkable how often the latter are of mononuclear rather than polymorphonuclear type. The ciliated epithelium may be desquamated and the mucous glands are distended with mucus and show marked catarrhal change. The lumen of the bronchus is filled with pus.

**Chronic Bronchitis.**—Chronic inflammation is a common condition, especially in damp climates. But it is seldom or never a primary entity, being rather a complication of some preëxisting pathological condition which may lie in the heart, the nasal sinuses, or the bronchi themselves.

*Chronic heart disease*, valvular or myocardial, is a common cause of chronic bronchitis on account of the continued congestion of the bronchial tree which weakens the resistance to bacterial invasion from the nose and throat. The *nasal sinuses* and *antrum* may serve as a constant source of infection, for septic material can so readily pass down the trachea and bronchi without ever being suspected.

*Dilatation of the bronchi* (bronchiectasis) is now known to be at the bottom of very many cases of chronic bronchitis, thanks to the diagnostic use of lipiodol. This subject will be discussed more fully in connection with septic diseases of the lung.

**Lesions.**—The mucous membrane may be swollen and hypertrophic, and bathed with mucus or pus. In old cases it may become atrophic, so that the wall has a reticulated appearance owing to strands of fibrous tissue which remains. Microscopically all the coats are infiltrated with round cells, but a replacement fibrosis which takes the place of the glands, muscle, and cartilage may be the chief feature. The epithelium is low and cubical, sometimes even flattened.

**Fibrinous Bronchitis.**—This is a rare and obscure condition in which the patient coughs up bronchial casts at periodic intervals. The casts are composed of mucin and epithelium rather than true fibrin. In diphtheria and pneumonia bronchial casts composed largely of fibrin may be formed.

### BRONCHIAL ASTHMA

The chief lesion in true asthmatics is a marked thickening of the wall of the smaller bronchi. All the coats are involved, but the muscular tissue is hypertrophied to a remarkable degree. The mucous glands are swollen and active, and the smaller bronchi may be blocked with mucus. During an anaphylactic attack the hypertrophied muscle

is thrown into severe spasm, the lumen is narrowed, and expiration becomes very difficult. This difficulty is increased by the narrowing of the lumen caused by the general thickening of the wall and the abundant secretion of mucus. The walls are infiltrated with chronic inflammatory cells, mostly eosinophils but with many lymphocytes. Eosinophils are found in other conditions where hypersensitiveness plays a part (infection with animal parasites, skin diseases, etc.), and their presence must indicate some kind of defense reaction. In some cases inflammatory lesions of the arteries have been observed similar to those of periarteritis nodosa. This is not surprising, as both diseases have an allergic basis. The lung may show areas of emphysema and atelectasis, the former due to the great strain thrown on the pulmonary tissue during the expiratory spasm, the latter due to absorption of air beyond bronchioles blocked by mucus. Elongated Charcot-Leyden crystals are often present in the sputum. They are believed to be derived from the eosinophils, and are also found in the tissues in leukemia and in the stools in amebic dysentery.

## THE LUNGS

**Descriptive Outline.**—In describing the lungs attention is paid to the pleura, pleural cavity, lung substance (color, air content, etc.), bronchi, pulmonary vessels, and bronchial lymph nodes. The *pleura* presents the usual smooth glistening surface of a serous membrane. The *pleural cavity* is nearly dry during life, but an appreciable amount of serous fluid may collect during a prolonged death agony, and in cardiac and renal disease there may be a remarkable accumulation during the last few hours of life. The lungs may be greater in *volume* than normal or they may be collapsed. The *weight* of the right lung is 350 to 550 grams, that of the left lung 325 to 450 grams. The *texture* is soft and pillowy. Owing to its *air content* it crepitates when pressed between the finger and thumb, and floats in water. These properties are lost when the air has been squeezed out of the lung by pressure from without or has been replaced by inflammatory exudate or edema. The apex should be inspected for the puckered scar of healed tuberculosis. The *color* depends on the amount of blood in the lung and on the amount of carbon pigment which has been inhaled. In the child the lung is of a uniform pink color, while in the adult it is of a dark slate-gray and shows varying degrees of pigmentation. The pleural lymphatics contain carbon, and thus outline in black the polygonal lobules which give the surface a mosaic appearance. On the cut surface the pigmentation follows the lines of the septa, the bronchi, and the arteries, and blackens any patches of scar tissue which may be present. In actual practice it is rare to find a lung that is perfectly normal throughout in color and consistency, because during the last hours of life blood tends to collect in the loose pulmonary tissue, and even after death blood gravitates to the dependent part of the lung, rendering it darker and firmer than normal. The *bronchi* are opened, their wall inspected for inflammation or tumor, and any contents noted. The *pulmonary vessels* are opened and examined for thrombi or emboli. Finally the condition of the *bronchial lymph nodes* is noted.

## LOBAR PNEUMONIA

Pneumonia signifies an inflammatory consolidation of the lung. When it is diffuse it is called lobar pneumonia, when nodular in type

it is known as bronchopneumonia. Pneumonias may also be classified on a bacteriological basis according to the infecting organism. Lobar pneumonia is a much more clear-cut pathological entity with constant etiology than is bronchopneumonia.

**Etiology.**—In over 95 per cent of cases the infecting organism is the pneumococcus. In the few remaining cases it is Friedländer's pneumobacillus, which produces a characteristic slimy type of exudate. In nearly three-quarters of the cases the pneumococci are Types I and II, more rarely Type III, and the remainder belong to Group IV, consisting of some 29 types. Since the introduction of the sulphonamide drugs the typing of pneumococci has lost much of its significance.

It is now believed by many observers that *allergy* plays an important part in the pathogenesis of pneumonia. Certain it is that the age period at which the disease is most prevalent is that at which there is a high level of humoral immunity. Immune bodies are best developed in early and middle adult life, and are present in minimal amount in early childhood when the disease is rare. When an animal is sensitized (not immunized) to a bacterial protein, subsequent injection of that protein into the trachea is followed by the same rapid extravasation of inflammatory fluid into the lungs as is seen in lobar pneumonia. Clinical observations also suggest that previous infections of the respiratory tract may sensitize the lungs so that pneumonia may be the result of a subsequent infection.

**Predisposing factors** lower the resistance of the patient and allow the organisms to pass from the upper to the lower respiratory tract. The best recognized of these are profound fatigue, chill, injury to the chest, severe fractures, debilitating diseases, and chronic alcoholism. In experimental alcoholism the leucocytes fail to show margination and do not emigrate, although their motility and phagocytic power are unimpaired (Pickrell).

**Route of Infection.**—Pneumococci reach the pulmonary alveoli *via* the bronchial tree. The earlier work of Blake and Cecil on monkeys seemed to suggest that the organisms penetrated the walls of the trachea and main bronchi, spread through the interstitial framework, and finally entered the alveoli, as it were, by the back door. More recent work by Loosli on the monkey and Robertson on the dog has shown that in experimental pneumonia the infection passes along the bronchi directly to the alveoli, and the same is almost certainly true of infection in man. The organisms pass in the inflammatory fluid from one alveolus to another through the interalveolar pores of Cohn. Thus the wave of infection sweeps throughout an entire lobe, but is often limited to that lobe. Spread of infection along the bronchial tree under the control of gravity is also of primary importance. Direction of spread depends on the bodily attitude of the sick person or animal. The capsular polysaccharide contains an edema-producing substance which can be extracted. It is natural, therefore, that the first feature of the exudate should be a marked inflammatory edema.

The mechanism by which the pneumococci are destroyed has been

demonstrated in a remarkably beautiful series of experiments by Barry Wood and his associates. The all-important element is the leucocyte, mainly polymorphonuclear, but macrophage in the later stages. The organisms are carried outward by the advancing flood of edema fluid, pursued in turn by the leucocytes. If the tortoise is to catch up with the hare the pace of the latter must be slowed down. This may be effected by means of specific antibodies which cause agglutination of the pneumococci or by the bacteriostatic action of the sulphonamides and penicillin. Antibodies (opsonins) are necessary for phagocytosis when the organisms are floating free in fluid, as in a test tube. They are not needed, however, in the lung. When the leucocytes have overtaken the pneumococci they pin them against the walls of the alveolar sacs, and only then are they able to engulf them. The organisms are soon digested and disappear, so that phagocytosis can only be observed in the outer edema zone and not in the densely consolidated inner zone. All of these phenomena can be seen in remarkable photomicrographs which illustrate Wood's papers.

**Symptoms.**—The clinical manifestations of lobar pneumonia are partly local, partly general. The former are pain in the chest made worse by breathing, signs of consolidation of the lung (dulness on percussion, blowing breathing, increased vocal fremitus and resonance), moist râles during the period of resolution, and blood-stained sputum. The general symptoms are fever, dyspnea, evidence of severe toxemia, and a marked leucocytosis. After a course of seven or eight days the illness suddenly terminates by crisis.

**Lesions.**—The essential pathological feature is an out-pouring of an inflammatory exudate into the alveoli in response to the irritation produced by the pneumococci. The alveoli are filled by this exudate, the air is displaced, and the lung or part of it is converted into a solid and airless organ. This process is known as consolidation or hepatization because the lung becomes like the liver (*hepar*) in consistence. Four stages are recognized for descriptive purposes: congestion, red hepatization, gray hepatization and resolution, but these are really of very little importance. What is important is to realize that the process is a progressive one commencing at the hilus and sweeping out to the periphery, involving one or more lobes and sometimes both lungs. It follows that one part of the lung may be at one stage while another part is at another. The stage of the process can be determined by noting the freshness or the reverse of the exudate.

The *gross appearance* of lobar pneumonia is very characteristic. (Fig. 192.) By the end of the second day the stage of *red hepatization* has been reached, and the affected part is consolidated, voluminous, reddish-brown in color, and sinks in water. It is very friable, so that the finger can be pushed into the solid mass. The surface is covered by a dull, fibrinous pleural exudate and the bronchi are intensely congested. The cut surface is dry, for the exudate in the alveoli consists of fibrin and cells. This dry surface is rough and granular and has been likened to red granite. The roughness is caused by plugs of fibrin projecting slightly above the surface. Only one part of a lobe may be

consolidated, and the line of separation between the two parts is remarkably sharp. When the stage of *gray hepatization* is reached, usually by the fifth day, the consolidated part is gray in color, more friable, and the pleural exudate is thicker. The cut surface is gray or brownish-gray, and it is now distinctly moist owing to softening of the exudate. The bronchial lymph nodes are enlarged and congested. In the stage of *resolution* (the stage of recovery), the lung has become soft and translucent, and may be almost jelly-like in consistence.



FIG. 192.—Lobar pneumonia. The upper lobe is completely consolidated, being in a state of gray hepatization. The lower lobe, only part of which is shown, is not involved.

The *microscopic appearance* depends much on the stage of the process. At the very beginning the capillaries in the alveolar walls are intensely congested, and large numbers of pneumococci lie in a fluid exudate. (Fig. 193.) The alveoli are soon filled by an acute inflammatory exudate, all the elements of which are sharply preserved. The two chief elements of the exudate are fibrin (lobar pneumonia is sometimes called fibrinous pneumonia) and polymorphonuclear leucocytes; the proportion of these varies much in different parts of the section. (Fig. 194.) Other constituents of the exudate are red blood



cells, some plasma which may not have been converted into fibrin, a certain number of lymphocytes and monocytes from the blood, and pneumococci. All of these are sharp and distinct. The alveolar walls and the interstitial tissues show marked congestion and edema, so that under a low power the section presents a mosaic appearance, the consolidated alveoli being separated by greatly thickened walls. Sometimes a capillary may contain a large multinucleated mass, which appears to be a megakaryocyte dislodged from the bone-marrow. The pleural surface shows an acute fibrinous exudate, and the lumen of the bronchioles is filled with pus.

Later in the process, corresponding to the stage of gray hepatization, degeneration and softening of the exudate takes place. The various constituents of the exudate have lost their freshness, the nuclei of the polymorphonuclears are blurred and indistinct, the red blood cells have vanished or

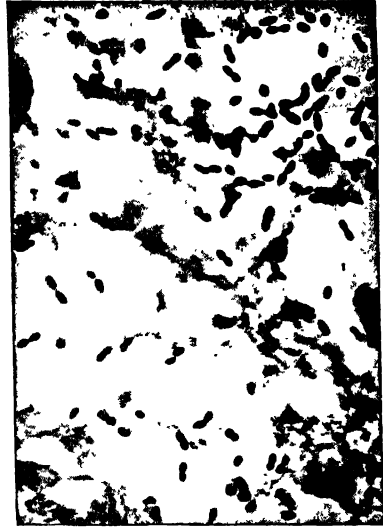


FIG. 193.—Lobar pneumonia, early stage. The alveoli, which are crowded with pneumococci, contain edema fluid but no leucocytes.  $\times 1300$ .

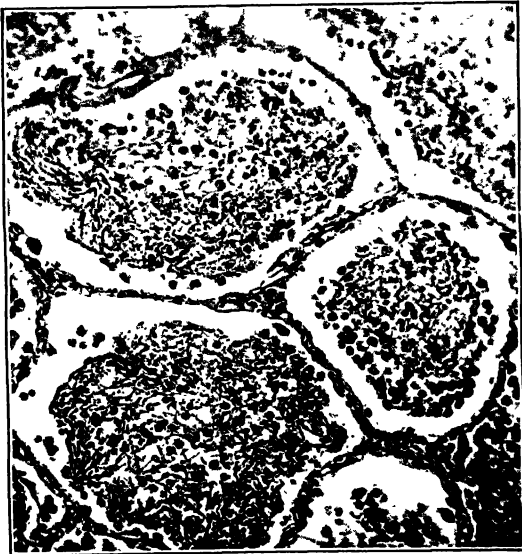


FIG. 194.—Lobar pneumonia. The alveoli are filled with an acute fibrinous exudate.  $\times 100$ .

appear as mere ghosts, and the threads of fibrin are clumped together into amorphous masses. The pneumococci can no longer be distinguished. In the later stages the mononuclear phagocytes or macrophages play a prominent part in the process (Robertson and Uhley). Although there is considerable difference of opinion on this point, it appears probable that the macrophages are derived chiefly from the hypertrophy and transformation into larger phagocytic cells of the lymphocytes and monocytes after they entered the alveoli along with polymorphonuclear leucocytes in the early stages of the disease (Loosli). In the experimental animal (dog) this transformation is complete by the end of thirty-six hours. The macrophages contain red blood corpuscles, pneumococci, and degenerated polymorphonuclears. The so-called septal cells become swollen and may project into the alveolar lumen in a remarkable manner, but they show no evidence of phagocytosis, nor do they become detached in any considerable numbers. The lymphatics in the interstitial tissue are filled with phagocytes on their way to the enlarged bronchial lymph nodes.

It is seldom that one sees the human lung in the stage of resolution, because by that time the patient is out of danger, but the process can be studied in the experimental pneumonia of monkeys. The exudate now consists of little more than disintegrating nuclei, granular débris, and mononuclear phagocytes. The fibrin is dissolved by proteolytic ferments, probably liberated by the disintegrating polymorphonuclear leucocytes. Once the exudate is softened it is removed partly by coughing, partly by being taken up by phagocytes and carried to the lymph nodes, but mainly by simple solution and absorption. Resolution is a remarkable process, for it converts a completely solidified lung back again into a perfectly normal organ.

**The Relation of Symptoms to Lesions.**—The *physical signs* are easily explained by the pathological findings. The dullness, blowing breathing, increased vocal fremitus and resonance are caused by a conversion of the lung into a solid organ which conducts sounds from the large bronchi to the chest wall with the greatest readiness. The moist râles heard during resolution are caused by the liquefied exudate in the bronchioles. The *pain* is due to pleurisy. It is an early symptom, because the pneumococci reach the surface long before consolidation has become complete. The *sputum* is rusty in color because it contains broken-down red cells. If there is much alveolar hemorrhage the sputum will contain bright blood. The sputum is very tenacious and stringy owing to its highly fibrinous character. The *blood* shows a high leucocytosis owing to the extensive character of the leucocytic exudate. Blood culture may be positive, but it is a sign of ill-omen except in the earliest stages. In cases which are going to recover the pneumococci usually soon disappear from the blood.

The *respiratory disturbances* (dyspnea, rapid shallow breathing, and in the more severe cases cyanosis) cannot be explained merely by the exudate in the lung, for they may be marked even though the pulmonary lesion is quite limited. They appear to be bound up with the condition of lowered oxygen saturation of the arterial blood known as *anoxemia*, the index of which is cyanosis. The means by which the anoxemia is produced is not certain. The presence of a layer of fluid on the inside of the alveoli will prevent the normal gaseous interchange in the lung. This is a factor of great importance in producing the cyanosis of influenzal pneumonia, but whether it plays a part in

lobar pneumonia we cannot be certain. A rise in the percentage of carbon dioxide in the inspired air acts as a powerful stimulant to respiration in a normal person, making it much deeper, but in pneumonia the respiratory center fails to react to this stimulus, a failure to which the anoxemia of the disease may be closely related.

The *crisis* is a clinical phenomenon which cannot be explained by the pathological lesions. It is the most dramatic of changes, for in a few hours the temperature may drop 7° to 8° F., the dyspnea disappears, the respirations return to normal, and the patient passes suddenly from a condition of grave peril to one of complete safety. And yet the lung is in the same condition before the crisis as after it. A sudden detoxication occurs, but the explanation must be sought on immunological rather than morphological grounds.

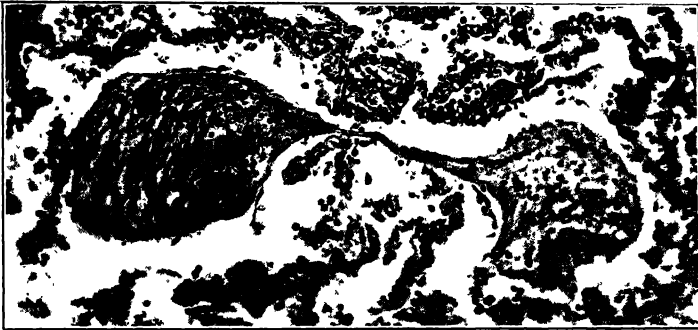


FIG. 195.—Organization of a pneumonia exudate. A strand of fibrous tissue passes through an opening in the alveolar wall.  $\times 150$ .

**Complications.**—*Organization* of the inflammatory exudate may occasionally occur. It becomes changed from fibrin into fibrous tissue. The strange thing is that this does not happen more frequently. Usually resolution occurs in time and the exudate melts away before fibroblasts have time to invade it. When organization occurs fibroblasts grow into the exudate from certain points of the alveolar wall, especially the angles, and these are soon followed by capillaries which later disappear. Long strands of fibrous tissue are formed which traverse the alveoli, often passing from one alveolus to another through what appear to be openings in the walls. (Fig. 195.) The end-result of these changes is to convert the lung into a dense elastic structure. As it is fleshy in consistence the process is known as *cornification*.

*Suppuration* and *abscess formation* are not common, and are due either to a very virulent infection or to poor resistance on the part of the patient. The alveolar walls are broken down and the exudate becomes purulent. It must be understood that although the exudate in lobar pneumonia may consist largely of polymorphonuclear leucocytes, this is not pus, and, as a rule, there is no suppuration, *i. e.*, breaking-down of tissue. Empyema may develop, but this is not common except in children, though a frequent complication of streptococcal pneumonia. Spread of the infection may also cause pericarditis. As a result of pneumococcal septicemia there may be endocarditis, meningitis, and arthritis.

## BRONCHOPNEUMONIA

This condition, also called lobular pneumonia on account of its patchy character, is not a definite entity like lobar pneumonia. It may be a primary disease, but more often it is secondary to some other infection. It occurs principally in childhood and old age. The susceptibility of the child may be due to poor expulsive power, to the delicate mucosa, or to the short wide bronchial tree. The pneumonias following measles, whooping cough and other infectious fevers are bronchopneumonic in type; so also are the postoperative and terminal pneumonias. It is usually due to streptococci, but pneumococci, staphylococci and influenza bacilli may be the predominant organisms. The pneumococci generally belong to Group 4. Infection is by way of the air passages, sometimes due to aspiration of septic material.



FIG. 196.—Streptococcal bronchopneumonia, showing patchy character of the exudate.  $\times 60$ .

There is a patchy consolidation of both lungs, a lobular pneumonia which can often be felt better than seen. Sometimes the patches fuse together, giving a confluent bronchopneumonia which may simulate lobar pneumonia. Collapsed areas, dark purple in color and depressed below the surface, are seen on the outside of the lung especially in children. The collapse is caused by the bronchioles becoming filled with secretion, so that the air cannot enter the lobule; the imprisoned air in the alveoli is then absorbed and the lobule becomes collapsed. The collapsed areas are surrounded by emphysematous bullae, a compensatory arrangement. A thin fibrinous exudate covers the surface. On the cut surface the patchy character of the lesions is very evident,

areas of consolidation alternating with areas of collapse, of emphysema and of normal lung tissue. The patchiness can be seen even better with the naked eye in a stained section. The consolidated areas are then seen to be grouped around small bronchioles. The bronchial lymph nodes are enlarged and soft.

*Microscopically* there is an intense inflammation of the bronchial wall, the lumen of which is filled with pus and desquamated epithelium. There is more of a bronchiolitis in streptococcal pneumonia than in the lobar form. The bronchiole is surrounded by a ring of alveoli filled with an inflammatory exudate consisting mainly of polymorphonuclear

leucocytes with a moderate amount of fibrin. (Fig. 196.) Farther out the alveoli contain mononuclear cells and edematous fluid. The consolidated areas alternate with areas of congestion, collapse, and emphysema.

Recovery is often not complete. The walls of the bronchi are damaged, granulation tissue is formed followed by fibrosis, and permanent bronchiectasis may result. Moreover there is no distinct crisis, and absorption of the exudate tends to be delayed so that organization may occur. In these respects the disease differs from lobar pneumonia, which is a more satisfactory and honest type of infection—provided the patient recovers.

### INFLUENZAL PNEUMONIA

The general problem of influenza and the question of its bacteriology have already been discussed in Chapter VII. The conclusion arrived at there was that influenza is due to a filter-passing virus assisted by *Bacillus influenzae* and other organisms. One of the greatest difficulties is to distinguish between the lesions of a pure infection and those due to secondary invaders. The influenza virus lowers the resistance to such a degree that secondary infection (*influenza bacillus*, streptococcus, pneumococcus) occurs with great readiness. It is these invaders which produce the pneumonic consolidation, although certain fundamental features of the lesions, common to all the forms, may be attributed to the action of the virus.

**Symptoms.**—The most characteristic symptoms of influenza are profound prostration, a dry hacking cough, and leucopenia in place of the usual leucocytosis of acute infections. In addition, in the more severe cases with pulmonary complications there may be cyanosis, dyspnea, watery blood-stained sputum, pleurisy, and not infrequently empyema.

**Lesions.**—It is difficult to speak with confidence of the lesions of a pure influenzal infection, because the number of cases on record in which influenza virus has been demonstrated at autopsy and the pathological changes described is incredibly small, and in fewer still have there been no bacterial invaders. From the work of Parker and his associates the essential features appear to be hemorrhagic edema together with a small amount of fibrin in the alveolar spaces and the formation of a hyaline membrane lining the alveolar walls. The lesions, indeed, are minimal. The almost universal occurrence of secondary bacterial infection gives rise not only to pneumonia but also to the necrotizing bronchitis and bronchiolitis so frequently seen. The trachea and bronchi are intensely congested, and the ciliated epithelium is desquamated, giving a "chevaus de frise" appearance (Fig. 197), thus opening the way to secondary invaders. The alveolar walls are thickened and infiltrated with lymphocytes and mononuclear cells. The bronchioles are filled with pus, their walls are damaged, and there may be subsequent dilatation and bronchiectasis.

The pneumonic lung varies in appearance, but the lesions are con-

stantly bilateral. At the height of an epidemic, and sometimes in sporadic cases, the lungs are voluminous, covered by a thin fibrinous exudate, and of a vivid red color with splashes of a dusky purple. From the cut surface pours a bloody watery fluid due to a hemorrhagic edema which is the outstanding feature of the condition. In a marked case a correct diagnosis can be made at a glance. The lung is heavy, but without the firm consolidation of lobar pneumonia or the nodular consolidation of bronchopneumonia. The most marked feature of the microscopic picture is edema fluid filling the alveoli, with numerous red blood cells but few leucocytes and no fibrin. The alveoli may occasionally be lined by a hyaline membrane apparently derived from the albuminous fluid within the alveolar spaces. In interepidemic periods the picture is less dramatic, but hemorrhagic edema is still



FIG. 197.—Trachea in influenza. Desquamation of epithelium, congestion of mucosa, and infiltration with inflammatory cells.  $\times 300$ .

the characteristic lesion. At the beginning of an epidemic, before secondary invaders have attained a high virulence, a nodular peribronchial interstitial pneumonitis may be the dominant lesion. Inflammatory cells may fill the alveoli as well as bronchial wall and interstitial tissue, so that small nodular lesions are produced which may resemble miliary tubercles.

*Streptococci* give rise to the most serious *secondary infections*. In the 1918 pandemic the common organism in the United States was *Streptococcus hæmolyticus*, while in the British Army it was *Streptococcus viridans*. The streptococcal lesions are likely to be lobular pneumonia, abscess formation, and empyema. *Pneumococci* produce a pneumonia which is often lobar in distribution but not lobar in type, because the influenzal toxins interfere with the leucocyte exudation

and fibrin formation characteristic of ordinary pneumococcal infections. In this form also empyema is common.

**The Relation of Symptoms to Lesions.**—The dry, hacking cough is due to the acute tracheitis and bronchitis. Cyanosis and dyspnea are probably due to interference with the exchange of gases in the alveoli, this in turn being caused by the copious outpouring of fluid. The watery, frothy, hemorrhagic sputum merely represents an external appearance of the hemorrhagic edema of the lungs. The profound prostration, the most striking of all the symptoms of true influenza, is due to the general toxemia. So also is the Zenker degeneration of muscle and other changes of a general character which are not discussed in this place.

### OTHER FORMS OF PNEUMONIA

**Terminal Pneumonia.**—Pneumonia may be found at autopsy as a termination of a chronic illness in which there is no hint of fever to suggest a pneumonic process. The consolidation is usually patchy in character and basal in distribution, so that it is often called hypostatic pneumonia. Hemorrhage and edema (hypostatic congestion) are common terminal conditions in the dependent parts of the lung and are often associated with terminal pneumonia. The inflammation is a mild one, and is due to the growth of organisms of low virulence in devitalized tissues rather than to invasion by virulent organisms. The bacteriology is of a very mixed description. The alveoli are filled with mononuclear cells together with a few polymorphonuclears, red blood cells, and much edematous fluid. There is a notable absence of fibrin, nor is there usually any pleurisy (hence the absence of pain).

**Postoperative Pneumonia.**—*Aspiration pneumonia* is due to aspiration of septic material during an operation; there is more danger of this during general anesthesia, but it may occur under a local anesthetic. Operations on the mouth and tonsils are the chief danger. Suppuration and abscess formation are common. The bacteriology is naturally very varied. *Aspiration of stomach contents* as the result of terminal vomiting produces a characteristic postmortem picture. Both lungs are of a dirty dark color, of soft almost mushy consistence, and have a sour, acid smell. The condition is of course not pneumonia but post-mortem digestion.

The work of Yandell Henderson, Coryllos, and others suggests that *atelectasis* may be an important factor in the production of postoperative pneumonia and possibly in other forms of pneumonia, especially in the new-born. When a patient lies on his back after a general anesthetic the bronchial tree tends to become filled with secretion so that the bronchioles are blocked. The free drainage by which the lung is kept in an aseptic condition is interfered with, the air distal to the obstruction is absorbed, the corresponding lobules collapse, and in the occluded area a mild pneumonia is likely to develop. Deep breathing induced by inhalation of carbon dioxide as suggested by Henderson and Hubbard is followed by opening up of the bronchioles, and may be used as a prophylactic against the development of postoperative pneumonia when it is especially feared.

Pulmonary embolism is another fairly common postoperative complication which need not be discussed here.

**Staphylococcal Pneumonia.**—This is an uncommon form of atypical primary pneumonia. The onset is often abrupt with chills, high remittent fever, and signs and symptoms first of bronchopneumonia and later of lung abscess. The sputum is yellowish, highly purulent, odorless, and swarming with staphylococci. The lesions are bronchopneumonic, developing later into multiple abscesses. The disease may appear in epidemic form with a high mortality.



FIG. 198.—Hyaline membrane in pneumonia of the new-born.  $\times 500$ .



FIG. 199.—Oil pneumonia; phagocytes filled with globules.  $\times 450$ .

**Pneumonia in the New-born.**—Pneumonia is a common cause of stillbirth. The infection, acquired *in utero*, may be due to inhalation of amniotic fluid or may possibly be caused by maternal infection. Many stillborn children show evidence of aspiration of amniotic fluid without definite pneumonia. Farber points out that the most important contents of this fluid are cornified desquamated epithelial cells from the skin of the fetus and vernix caseosa which is rich in fat and fatty acids. In the alveoli the desquamated epidermal cells take the form of long wavy structures with pointed ends. The vernix caseosa is pressed tightly against the walls of the alveoli and bronchioles as the result of inspiratory efforts by the child, and resembles the inflammatory “hyaline membrane” of influenzal pneumonia which is formed from albuminous intrapulmonary fluid in very much the same way. (Fig. 198.) This vernix membrane stains red with eosin, and red with scharlach R. in frozen sections owing to its fatty nature.

**Chemical Pneumonia.**—During World War I poison gas often produced acute pulmonary lesions much like those of influenzal pneumonia. There was the same acute hemorrhagic edema, and the patients were often literally drowned in their own fluids. If the patient recovered the lungs were permanently damaged and liable to recurring infections.

**Lipoid Pneumonia.**—This term denotes an inflammatory condition of the lung caused by the presence in the alveoli of animal or mineral oil. It may



develop when the throat has been repeatedly sprayed with mineral oils, liquid petrolatum, etc., especially in children. The habitual forced administration of cod-liver oil in children is another cause. It is important to realize that light oils can pass with ease from the upper respiratory passages to the lungs. The condition is much commoner than has been suspected, the incidence having increased greatly since the existence of the lesion was first demonstrated by Laughlen in 1925. This is due to the widespread habit of self-medication by the public who so frequently use oily sprays or drops for upper respiratory infections. Animal oils, particularly cod-liver oil, are highly irritating. Liquid petrolatum, although less acutely damaging, produces severe chronic effects, as it leads to the formation of reticulum fibers, giant cells, and finally extensive fibrosis. In the gross the affected areas are gray or yellow and moderately firm, projecting slightly above the pleural surface. The patches become firmer and grayish-white, and may be mistaken for tumor metastases. The alveoli are filled with large phagocytic cells (lipophages) distended with droplets of oil, giving a highly characteristic microscopic picture. (Fig. 199.) It must be pointed out that macrophages filled with lipid may be present in the alveoli apart from true lipid pneumonia. They are seen in pulmonary tuberculosis, chronic suppuration, and in the vicinity of large infarcts. In such cases the lipid must be of endogenous rather than exogenous origin. Liquid petrolatum stains with scarlet red but does not reduce osmic acid, whereas cod-liver oil reduces osmic acid. In the later stages fibrosis is marked, and giant-cell formation is common. The disease occurs at the two ends of life, and the adult form is characterized by a dense fibrosis which is often so clearly localized that it may be mistaken for a neoplasm (paraffinoma of lung).

**Virus Pneumonia.**—Pneumonia, or rather pneumonitis, may occur in a number of virus diseases. The more important of these are influenza, psittacosis, Australian Q fever, and the so-called primary atypical pneumonia. The great difference between virus infections of the lung and bacterial pneumonias is that in the former the chief lesion is an interstitial inflammation, as evidenced by lymphocytic and mononuclear infiltration of the walls of the bronchioles and the lung framework with a varying degree of alveolar edema, whereas in the bacterial pneumonias the cellular and fibrinous exudate occupies the alveolar spaces.

*Primary atypical pneumonia*, often referred to specifically as virus pneumonitis, is a new arrival in the infectious field. The infection causes an acute inflammation of the mucous membranes of the upper respiratory tract, occasionally extending to the trachea and bronchi and in a few cases to the bronchioles and lungs. The morbidity is high, but the mortality low. The physical signs are largely negative, but there is roentgen-ray evidence of a patchy, ill-defined consolidation, seldom involving more than a portion of a lobe. The course is usually mild, lasting two or three weeks, and a fatal outcome is rare. Inoculation of all the laboratory animals proved negative, but Weir and Horsfall found that in the mongoose a pneumonia was produced which was bacteriologically sterile. This pulmonary lesion was marked by extensive edema of the alveoli and alveolar walls, together with small numbers of mononuclear cells. The virus is readily propagated on the chorio-allantoic membrane of the chick embryo. In new-born children a form of epidemic pneumonia has appeared which is apparently due to a virus. It is highly contagious, the mortality is high, and cytoplasmic inclusion bodies are present in the bronchial epithelium.

**Mucosal Respiratory Syndrome.**—This descriptive term, suggested by Stanyon and Warner, has been applied to a condition characterized by inflammatory lesions of mucous membranes, skin and lung, and caused almost certainly by a virus. The condition is sometimes referred to as the Stevens-Johnson syndrome. The mucous membranes involved are those of the mouth, conjunctiva, and genital tract. The onset and spread of the stomatitis is rapid and dramatic, and within a few hours the mouth is a mass of large, shallow, extremely painful ulcers. The lungs are consolidated by what is evidently a

virus pneumonia, with great edema, an alveolar exudate consisting entirely of mononuclear cells, extreme swelling of the alveolar lining cells, loss of bronchial epithelium, and mononuclear infiltration of the bronchial walls. In some cases there are erythematous or hemorrhagic lesions of the skin.

**Löffler's Pneumonia.**—The condition usually known as Löffler's syndrome, first described in 1932, is characterized by a mild clinical course, marked eosinophilia, and transitory pulmonary lesions which present a remarkable and alarming picture in the x-ray films. Little is known about the pathological lesions, because the patient seldom dies. In a careful study by Bayley, Lindberg and Baggenstoss, the following changes were observed. Scattered throughout the lungs were focal areas of consolidation. Some of these consisted of fibrous tissue with an intermingling of great numbers of eosinophilic leucocytes, whilst others presented a granulomatous picture with epithelioid cells, numerous eosinophils, and fibrinoid degeneration of collagen. Wide-

spread vascular lesions were present, in particular a necrotizing arteritis similar to that seen in periarteritis nodosa. In the bronchi there was marked hypertrophy of the muscle and extensive eosinophilic infiltration, lesions identical with those of bronchial asthma. The entire picture is strongly suggestive of an allergic reaction. The allergic agent may not be the same in every instance. In some cases the larvæ of *Ascaris lumbricoides* which migrate through the lungs may be responsible, whilst in others the antigen responsible may be pollens or bacteria.

**Giant-cell Pneumonia.**— This condition, first described by Hecht in 1910, is an interstitial pneumonitis of infants and young children characterized by the presence of large multinucleated giant cells. It has been suggested by Chown that it is a manifestation of vitamin A deficiency. Pinkerton and his associates describe cell inclusions, both cytoplasmic and intranuclear, in several cases, and point out the close resemblance of the lesions to



FIG. 200.—Fetalization of alveolar lining.  
× 160.

those of dog distemper. For this reason they believe the condition to be due to infection by a virus, possibly closely related to that of distemper. It is possible that the cellular disturbance produced by the virus may render impossible adequate utilization of vitamin A.

**Radiation Pneumonitis.**—When the chest is exposed to repeated doses of therapeutic radiation reactive changes may occur in the lungs. The alveolar lining cells enlarge, and some become very hypertrophic and bizarre-like tumor giant cells. The bronchial epithelium shows similar but less extreme changes. The elastic tissue is ruptured and reduplicated. The alveoli may be lined by a hyaline membrane similar to that seen in epidemic influenza and in the new-born. The triad of epithelial hyperplasia, changes in the elastic tissue, and hyaline membrane lining the alveoli is pathognomonic. Injury to the tissues may lead to infection followed by fibrosis.

**Chronic Interstitial Pneumonia.**—An increase in the fibrous framework of the lung known as chronic interstitial pneumonia (a poor name) may be the result of an acute or a chronic process. An acute streptococcal or influenzal pneumonia may be accompanied by destruction of tissue and subsequent fibrosis, as a result of which the fibrous tissue around the bronchi and bloodvessels in the interlobular septa and under the pleura is much increased. The organization which occasionally follows pneumococcal pneumonia comes into a different category. The process may be chronic from the outset, as in the fibroid forms of tuberculosis and in the interstitial pneumonia of congenital syphilis. In the latter condition, known as pneumonia alba, the lung is pale, heavy, and consolidated. As a result of the irritation produced by the spirochetes an abundant granulation tissue is formed which separates the alveoli widely. In this and in other fibroid conditions of the lung the alveolar epithelium becomes cubical (usually it is invisible), so that the alveoli assume a gland-like appearance like that of the early fetal lung (Fig. 200), probably because of loss of respiratory function.

### THE PNEUMOCONIOSES

The long-continued inhalation of certain irritating dusts may cause a chronic interstitial pneumonia known as pneumoconiosis (*konis*, dust). The outcome of these dust diseases is entirely dependent on the presence and amount of silica in the dust. The dangerous pneumoconioses are silicosis and asbestosis, both of which may be disabling or fatal. Anthracosis, a condition caused by the inhalation of carbon in coal dust, is harmless in comparison.

**Silicosis.**—Silicosis is the most widespread, the most serious, and the oldest of all occupational diseases. Silicon (Si) is the most widely distributed element in nature. The silicates merely give rise to a foreign body reaction, but silica ( $\text{SiO}_2$ ), like asbestos, causes a progressive productive reaction ending in fibrosis and associated with marked impairment of pulmonary function. This condition, known as silicosis, is the most important of the dust diseases, and provides a serious hazard in the gold-mining industry in certain districts such as the South African Rand and northern Ontario. The worker is in great danger, but men mining any type of coal are liable to develop silicosis. If, in coal mining, hard rock has to be drilled through, coal-miners may also suffer. Other occupations in which there is danger are tin-mining, stone-working, metal-grinding and sand-blasting. In all of these cases dust containing fine particles of silica may be inhaled over long periods of time.

The particles of silica are taken up from the bronchioles, the epithelium of which is not ciliated, by phagocytes which carry them to the tiny lymphoid aggregations in the alveolar septa. The cell containing the silica undergoes changes similar to those seen in tuberculosis. The cytoplasm increases in amount and comes to contain lipid droplets, whilst the nucleus may divide repeatedly, so that a typical

Langhans giant cell may be formed. When silica is injected subcutaneously it produces necrosis, and the slow reaction in the lung results partly in necrosis but to a much greater degree in fibrosis. Both the rate and the extent of the fibrosis are in inverse proportion to the size of the silica particles. Previous disease processes, such as pneumonia, which may cause scarring of the delicate alveolar walls and lymphoid collections will facilitate the arrest of the particles and predispose to the production of silicosis. The fibrosis is at first patchy, corresponding to the deposits of silica in minute lymph follicles adjacent to the terminal bronchioles, and takes the form of "silicotic nodules" (Fig. 201), composed of concentric layers of fibrous tissue and readily palpated in the lung. These nodules gradually coalesce, and the fibrosis becomes widespread. In extreme cases the lung becomes stony hard, and in one instance I had to saw the lung in two. When the



FIG. 201.—Silicosis showing characteristic fibrous nodules.  $\times 13$ .

lesions are produced by pure silica dust, as in gold miners and sand blasters, the nodules have the clean-cut, laminated, onion-like character described above. When, however, as is frequently the case, the silica is mixed with other dusts, as in granite workers and anthracite coal miners, an interstitial fibrosis is added, and tongue-like projections extend from the nodules into the surrounding tissue. Moreover dust inclusions are commonly seen when the lesion is due to mixed dusts; these are seldom present in cases of pure silicosis. Emphysema is a common consequence of the extensive fibrosis, most marked, as a rule, at the base. The lymph nodes at the root of the lung are small, hard and fibrosed, with fibroblasts arranged in a characteristically whorled manner. The pleura is thickened and adhesions are common, due to deposits of silica in the subpleural lymphatics. The functional capacity of the lungs is greatly interfered with, and the chief symptom

is marked dyspnea. The necrotizing action of the silica may lead to destruction and cavitation, but these changes are usually due to an accompanying tuberculosis.

Most silicotics die of tuberculosis because the presence of silica in the tissues favors the growth of tubercle bacilli to an astonishing degree. This was shown by Gye and Kettle, who injected a mixture of silica and tubercle bacilli into mice and observed very rapid development of the tuberculous lesion. When silica is injected subcutaneously and tubercle bacilli are injected intravenously on the following day the same effect is observed. The tuberculous infection to which the patient succumbs may be acquired before or after exposure to silica dust. The lesions of silicosis and tuberculosis are essentially similar. In human cases it is often impossible to be certain of the nature of a given lesion when the two are combined. Silica can cause every type of cellular reaction found in tuberculosis. As Gardner remarks, it is strange that a simple inorganic compound like silicon dioxide can give rise to the same cellular reactions as the tubercle bacillus with its proteins, carbohydrates and lipoids.

The *radiological appearance* is of great importance, because it forms the basis for the clinical diagnosis. The earliest change is an increase in the normal reticulation of the lung. The specific appearance, however, is that of clean-cut nodules scattered widely throughout both lungs, but in cases due to mixed dusts the outline of the nodules is much more hazy. When calcium is deposited in the nodules they stand out still more sharply. When tuberculous infection is added the nodules develop a fluffy outline, increase in size, and eventually coalesce to form large shadows; this is in contrast to pure silicotic lesions which may remain discrete for years.

A possible explanation is suggested by the work of Fallon, who found that a phospholipid could be extracted from early experimental silicotic lesions. This is supposed to come from disintegrating mononuclear and epithelioid cells called forth by the quartz particles. When the phospholipid is injected into rabbits it produces a fibrotic reaction similar to that caused by finely particulate quartz and also similar to the lesion caused by the injection of the phospholipid fraction of tubercle bacilli.

Silicotic lesions are not confined to the lung. Silica may occasionally be carried to the liver and spleen, where it causes necrosis and fibrosis (Lynch).

**Anthracosis.**—A varying amount of coal dust is found in every lung at autopsy, and is usually of no significance. By itself coal dust appears to produce no harmful effect. In coal miners, however, it may give rise to the form of pneumoconiosis known as anthracosis. It does so because of the admixture of a certain amount of silica. In this mixed form the characteristic lesion is *dust-reticulation* (Belt), with corresponding fine net-like shadows (reticulation) in the roentgen-ray picture. Dust-reticulation is scattered diffusely throughout the lungs, forming a lace-like pattern along the lymphatic pathways and de-

pots in which dust-laden macrophages are entrapped. The appearance of innumerable dust-ridden cobwebs is due to the formation of fine argyrophil reticulum fibers; there is none of the collagen formation so characteristic of pure silicosis. The bronchial lymph nodes are masses of coal dust. In more advanced cases, which may be termed anthraco-silicosis, there may be *nodulation*, the formation of tiny nodules from 2 to 5 mm. in diameter. Finally there may be *confluent fibrosis*, a patchy confluence of the previous lesions. All of these features are due to the presence of the silica rather than the coal dust. Emphysema may be marked, due perhaps to destruction of the elastic tissue. Belt remarks that the collier's lung is in a very real sense his occupational log book; it retains a qualitative and an indelible record of the mineral particles breathed during life.

FIG. 202. — Asbestos body showing globular ends and segmented appearance. (Specimen of Dr. J. E. Pritchard.)

**Pulmonary Asbestosis.**—This condition is due to the inhalation of asbestos dust which may contain over 50 per cent of silica. The disease is acquired either during the crushing of asbestos rock or in the process of carding the asbestos. The lung shows the airless and fibrosed condition found in silicosis, and on the cut surface there are areas of caseation with cavity formation. The characteristic microscopic feature, in addition to a large amount of silica dust, is the presence of large angular particles which are probably fragments of asbestos fibers, and curious golden-yellow bodies with a globular end and segmented body. (Fig. 202.) The latter structures, which

may be called asbestos bodies, are pathognomonic of the condition, but their exact nature is not understood.

**Pulmonary Fibrosis of Uncertain Nature.**—Occasional cases are encountered by every pathologist in which there is more or less extensive interstitial fibrosis without any satisfactory explanation. They may be associated with a marked degree of compensatory emphysema. Some of these cases may represent healed disseminated miliary tuberculosis infected from an extra pulmonary source. In others there may have been a previous virus infection which damaged the pulmonary framework. Hamman and Rich report 4 cases of *acute* interstitial fibrosis of the lungs in which the pathological process was evidently rapid with accompanying right-sided heart failure. Belt describes fatal pulmonary fibrosis due to industrial exposure to radium over a period of two years. It is probable that there are other still unsuspected etiological agents.

### SUPPURATIVE CONDITIONS OF THE LUNG

Septic diseases form along with the pneumonias and tuberculosis the great trio of pulmonary infections. Many cases of supposed tuberculosis in which tubercle bacilli can never be found in the sputum belong to this group. The use of the bronchoscope and of lipiodol in the investigation of the bronchial tree has served as a great stimulus to the study of these diseases. The chief of these septic or suppurative conditions are abscess, gangrene, and bronchiectasis.

**Abscess and Gangrene.**—There is no sharp line to be drawn between abscess and gangrene of the lung. The former is a suppurative condition more or less circumscribed, while the latter is putrefactive and tends to be diffuse.

**Etiology.**—The cases may be divided into three groups: the inhalation, the embolic, and the pneumonic, depending on the method of causation.

1. The *inhalation group* is far the largest and most important. Abscess of the lung is a constant threat in operations on the mouth, nose, and throat. Tonsillectomy being the commonest operation is most often complicated by pulmonary sepsis, but this may happen with the removal of adenoids, operations on the nose, and the removal of teeth, and it may follow a local as well as a general anesthetic. The chief feature of the bacteriology of the inhalation group is its mixed character. This is in contrast to embolic abscesses or those due to staphylococcal pneumonia in which cases there is often only one infecting organism. The abscess is commoner in the right lung, perhaps because this lung has a more vertical bronchus. Foreign bodies may pass down the bronchial tree and give rise to abscess formation, especially in children. Septic material from the nasal sinuses, food regurgitated during general anesthesia, etc., may pass down the bronchial tree and cause an abscess. These foreign body abscesses must be distinguished sharply from other forms, because if the foreign body can be removed by means of the bronchoscope the prognosis is remarkably favorable. A metallic foreign body tends to cause hyperplasia rather than liquefaction of tissue, and when it is removed a complete cure may result. A sterile embolus may give rise to an abscess of the inhalation type, for obstruction of the vessel leads to extravasation of blood and fluid and an increase of bronchial secretion, a condition readily liable to infection from the bronchial tree.

2. The *embolic group* is caused by particles of a septic thrombus being carried to the lungs. As these particles are numerous the abscesses are nearly always multiple. The original septic focus may be in the lateral sinus, in the female pelvic veins, etc. If the embolus is large a septic infarct is produced which breaks down to form an abscess; if it is small no infarct is produced.

3. The *pneumonic group* is usually streptococcal. In streptococcal bronchopneumonia abscess formation is not uncommon, especially in those cases which complicate influenza. In lobar (pneumococcal) pneumonia, on the other hand, it is very rare for the consolidated area to develop into an abscess.

There remains a miscellaneous group where infection may spread from a neighboring organ, *e. g.*, the esophagus, the vertebral column, or from below the diaphragm. Bronchiectatic abscesses form a group which will be considered separately.

**Symptoms.**—The chief clinical manifestations of abscess of the lung are (1) cough and copious expectoration of pus, (2) foul breath and sputum

(3) elastic tissue in the sputum, (4) dulness on percussion. The signs of gangrene are the same as those of abscess, and often the two conditions are combined.

**Lesions.**—Abscess is commoner in the right lung, and is as frequent in the upper lobe as in the lower. The lesion is at first a solid mass of yellow inflammatory tissue, but as liquefaction occurs a cavity is formed filled with pus. This cavity may be of any size, from the smallest to the largest. The wall is ragged and necrotic, but in the more chronic forms a wall of fibrous tissue is built up and the lining becomes smooth. Owing to the close relationship in the pulmonary lobule between the bronchus and bloodvessels thrombosis is frequent, and this leads to extensive necrosis. The abscess is usually single at first, but secondary abscesses may occur at any time due to aspiration of infected material into other segments. The inhalation abscess is likely to communicate with a bronchus, the embolic abscess is not. Because the abscess is in the periphery of the lung the communicating bronchus is always small, rarely exceeding 2 to 3 mm. in diameter. A chronic abscess may show epithelialization of its wall from the bronchus. The *microscopic appearance* is that of an acute abscess with dense infiltration of polymorphonuclear leucocytes and a varying number of mononuclear phagocytes. The alveolar walls are destroyed, whereas in pneumonia they are preserved. As the condition becomes chronic fibroblasts multiply, and a wall of fibrous tissue is built up around the abscess.

The *odor* of the contents depends largely on whether the lesion is a merely suppurative or a gangrenous one. In an abscess uncomplicated by gangrene the contents may be inoffensive, but when gangrene supervenes the smell is horrible. This is due to decomposition of the proteins by saprophytes, of which the most abundant are *spirochetes* and *fusiform bacilli*, which are found in the contents of the cavity, in the sputum, and in sections of the lung. They are largely responsible for the necrosis. These organisms are secondary invaders from the mouth, where they occur in connection with carious teeth and pyorrhea. Some workers believe that they can act as primary invaders and produce the lesions unaided, but this appears improbable.

*Gangrene* may be preceded by abscess formation or may be the primary condition owing to the aspiration of heavily infected material. In debilitated persons a pneumonia may become gangrenous. Soft green areas are formed, and these break down with the production of ragged cavities filled with foul-smelling stuff. Bloodvessels traversing the cavity may be opened, sometimes with fatal hemorrhage. Gangrene of the lung is likely to be rapidly fatal.

**The Relation of Symptoms to Lesions.** - Pus may be expectorated in large amount, but this depends on whether the abscess communicates with a bronchus. Such a communication exists in bronchiectasis, in an inhalation abscess, and when an abscess bursts into a bronchus. If the abscess can be drained by means of the bronchoscope or even by effective coughing it may become healed. In an embolic abscess there is no communication with a bronchus, so



that no pus is expectorated. The *sputum* may be very characteristic, thick, purulent, yellowish-green in color, and often very abundant. On standing it separates into an upper frothy layer, a middle cloudy layer, and a lower deep purulent layer. The odor depends on the degree of putrefaction and gangrene. *Elastic tissue* in the sputum indicates destruction of the lung. It may show an alveolar arrangement, and is best demonstrated by dissolving the sputum in weak, warm potassium hydroxide, which leaves the elastic fibers unaltered. *Pleurisy* is common, because the abscess is often subpleural in position. *Empyema* may be caused by rupture of the abscess into the pleural cavity. *Brain abscess* is a common complication due to septic embolism. Two curious points should be noted: (1) that the cerebral abscess is often single, and (2) the nearly invariable absence of abscesses in the other organs. It is probable that the route of infection is by the vertebral series of veins described by Batson and others (page 258).

**Bronchiectasis.**—A dilatation of the bronchi, either local or general is known as bronchiectasis. Stagnation of the bronchial contents follows the dilatation, with resulting infection and suppuration. Minor degrees of the condition are common, although often missed clinically unless lipiodol is used.

**Etiology.**—The two main factors are infection and bronchial obstruction. The *infection* causes chronic inflammation of the bronchial walls with destruction of the musculo-elastic tissue resulting in dilatation of the part of the bronchial tree whose walls are damaged; the pathogenesis is the same as that of aortic aneurism. The dilatation favors accumulation of secretion with added infection and further injury to the bronchial wall. There may be a physiological block due to paralysis of the cilia from infection or metaplasia of the columnar epithelium into a squamous type, thus interfering with the normal mechanism for the removal of secretion (Robinson). A marked obliterating endarteritis may still further lower the resistance of the bronchial walls. In young children the process tends to be more acute, so that the first lesion is an ulcerative bronchitis with secondary destruction of the bronchial wall (Erb).

The acute infection, commonly occurring in childhood, may be measles or whooping cough, and occasionally influenza or pneumonia. The actual onset of symptoms is insidious, and is not ushered in by any acute illness. Neither gross upper respiratory tract infection nor chronic bronchitis is a common cause of bronchiectasis. Spirilla and fusiform bacilli are frequently found in the walls of the dilated bronchi, but it seems more probable that these are secondary invaders than primary etiological agents.

(*Obstruction* of the bronchi leads to accumulation and stagnation of secretion, infection and weakening of the bronchial wall. The obstruction may be due to carcinoma, a foreign body, or pressure from without by aneurism, etc.

**Lesions.**—Bronchiectasis may be diffuse (cylindrical form) or localized (saccular form). The former is the more common. (Fig. 203.) It is usually bilateral, but it is rather remarkable that quite often it is unilateral. For some unknown reason the left lung is more often involved than the right, and the lower lobes more often than the upper



FIG. 203.—Bronchiectasis. The bronchi show marked cylindrical dilatation.

owing to stasis. Only one lobe may be affected. The size of the cavity depends on the size of the bronchus. It is filled with pus which stagnates there owing to insufficient drainage, and still further weakens the wall of the bronchus. The mucosa is hypertrophic and may form tumor-like, highly vascular papillary masses. Later there may be atrophy. The *microscopic appearance* is similar to that of chronic abscess. The wall of the bronchus and the surrounding tissue is infiltrated with chronic inflammatory cells. The mucosa may be hypertrophic or atrophic, and in advanced cases the muscle, glands, elastic tissue, and even the cartilage may be replaced by fibrous tissue. (Fig. 204.) The most significant lesion is the destruction of the bronchial musculature and elastic tissue, for it is these which weaken the wall and allow the dilatation to occur. Septic thrombosis may occur with embolism and the formation of a secondary brain abscess.

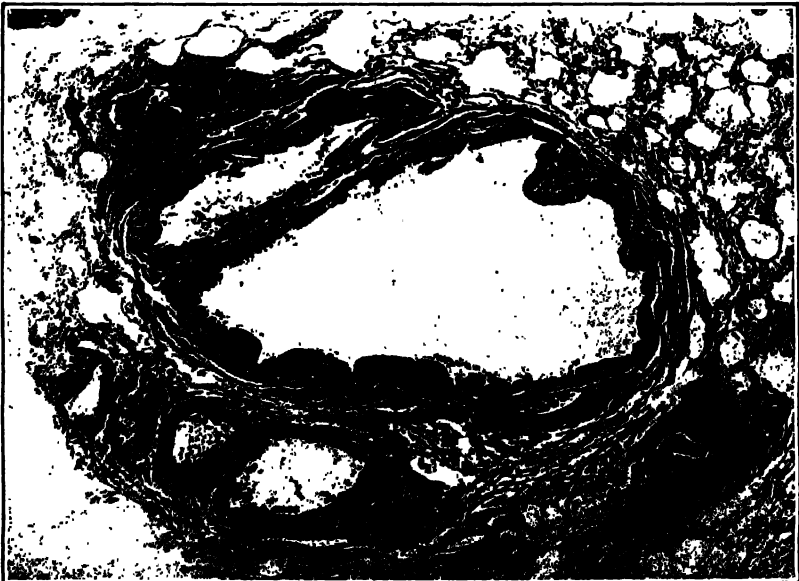


FIG. 204.—Bronchiectasis. Several small bronchi are dilated; their walls show fibrous thickening.  $\times 12$ .

**The Relation of Symptoms to Lesions.**—The chief symptom is due to the chief lesion, the patient bringing up large quantities of *pus* at infrequent intervals, often when he changes position (postural coughing due to the pus coming in contact with a new and more sensitive part of the bronchial wall) or on awakening in the morning. During the intervals the pus is accumulating. The character of the pus has already been described in connection with Abscess.

*Hemorrhage (hemoptysis)* is common, occurring in 50 per cent of the cases, and is due to the highly vascular papillary masses of mucosa which may line the cavity or to erosion of vessels passing through the cavity. *Lipiodol* introduced into the bronchial tree outlines with beautiful distinctness the bronchial dilatations in a roentgen-ray picture, and has served to show the bronchiectatic nature of many cases of supposed tuberculosis and chronic bronchitis.

**Congenital Bronchiectasis.**—This rare condition is often called *congenital cystic lung*. It occurs in children. The lung is occupied by cysts of varying size lined by epithelium which may be cubical and ciliated or flattened. The condition is probably a congenital dilatation of the small bronchioles. The bronchi develop as mesodermal buds which become canalized. If canalization does not occur at some point, but does occur distal to that point, an isolated segment will be formed lined by bronchial epithelium which secretes fluid and forms a cyst. The cyst may be single or multiple, small or large. The child suffers from severe attacks of dyspnea and cyanosis due to rupture of a superficial cavity and the production of a spontaneous pneumothorax. One of these attacks is likely to be fatal.

## TUBERCULOSIS OF THE LUNGS

The general problem of tuberculosis has already been discussed in Chapter VII, and in order to avoid needless repetition the reader is referred to that account for a consideration of such questions as the method of infection, primary and secondary infection, the relation of the type of lesion to the age of the patient, etc. Some of the conclusions will be briefly summarized here.

Tuberculosis of the lungs is the commonest of all forms of tuberculosis, partly because by whatever route the bacilli enter the body they pass *via* the lymphatics to the venous blood stream and thus reach the lungs, partly because the lungs are especially exposed to direct infection. In the adult the infection is nearly always of the human type, and is therefore acquired by inhalation. The inhaled material may be infected dust or infected droplets of sputum. Children may place infected material in the mouth and this may be inhaled into the bronchioles and alveoli.

The *incubation period* in so chronic a disease as pulmonary tuberculosis is difficult to determine, but it may be much shorter than anticipated as the following case in my own experience illustrates. A young man's tuberculin test was negative on June 25th. On July 12th he commenced animal experiments involving the use of living tubercle bacilli. On August 8th he developed general symptoms suggestive of infection and slight pain in the chest on breathing. On August 24th the tuberculin test was positive, on September 4th the roentgen-ray film was positive, and on October 17th the sputum contained tubercle bacilli.

Infection may *spread* from the original focus by the lymphatics, air passages, and blood stream.

1. *Lymphatic spread* is of special importance in the primary form. The lymphatics are perivascular and peribronchial and so are the lesions, which form a staphyloid group of tubercles around a central artery or bronchus. Such groups are often seen in the neighborhood of a caseous area. One of the tubercles may break through the wall of the bronchus or artery and rupture into its lumen causing a bronchial or blood spread of the infection.

2. *Bronchial spread* may occur when a focus opens into a bronchus (Fig. 205), and during the later stages infected material must be continually inhaled from one part

of the lung to another, setting up fresh areas of bronchopneumonia. The massive forms of tuberculosis such as tuberculous caseous pneumonia are mainly due to this bronchogenic spread.

3. *Hematogenous spread* is caused by rupture of a focus into a bloodvessel, usually a vein. This may cause miliary tuberculosis of the lungs as well as throughout the rest of the body.

The question of primary and secondary infection (re-infection) and the relation of age to the type of lesion are closely connected. It is customary to speak of the childhood and adult types of infection, but it is time that these terms are given up. The primary complex, *i. e.*, the reaction in tissues not sensitized to tuberculo-protein, used to develop in nearly every child, but now in many places



FIG. 205.—Tubercle rupturing into a bronchus.  
× 65.

not more than 10 or 15 per cent of children develop the infection, as shown by the tuberculin test. More primary infection now develops in adults than in children, and it is equally harmless in the great majority of cases. Primary infection is characterized by the Ghon lesion, seen in its active form in the child, in its healed (calcified) form in the adult. The secondary lesions of reinfection show a great variety of types, depending on the size of dose and the degree to which allergy or immunity happens to dominate the picture. The distinction between these two processes has already been insisted on in the general discussion of tuberculosis.

**Symptoms.**—The symptoms of pulmonary tuberculosis are both general and local. The chief *general* symptoms are fever, loss of weight, asthenia, night sweats, and anemia. Among the *local* symptoms are cough, expectoration, hemoptysis (spitting of blood), and pain in the side. There are *physical signs* of consolidation of the lung and cavity formation.

**A. Primary Infection.**—The primary lesion is a small caseous focus, seldom more than 1 cm. in diameter, usually though not always single, and situated in any part of the lung. In this it contrasts sharply with the secondary lesion which nearly always makes its first appearance at the apex. The primary lesion may be in the lower lobe and is often at the periphery of the lung. (Fig. 206.) The caseous center becomes surrounded with a fibrous capsule. Calcification and sometimes ossification occur, and the healed lesion is represented by a small scar or calcified nodule. Foci in the regional lymph nodes also become encapsulated and calcified, but some caseous material usually persists and may harbor viable tubercle bacilli for many years. Spread occurs primarily along the lymphatics, so that the regional lymph nodes are enlarged and caseous, again in contrast to what is found in secondary lesions. A chain of tubercles can be traced from the primary lesion to the infected lymph nodes. One of the caseous nodes may open into a blood-vessel and cause general miliary tuberculosis.

The patient with primary infection either recovers or dies; the disease does not become chronic, nor is there any cavity formation. If recovery takes place there is healing of the pulmonary and the glandular lesions by encapsulation with subsequent calcification. These healed primary lesions are most readily detected at autopsy by taking roentgen-ray pictures of the lungs, but calcified subpleural nodules may also be felt. Sometimes actual bone is formed in the primary lesion. The results of healing are: (1) calcified parenchymal and lymph node foci; (2) a state of allergy shown by the tuberculin test. About one-half of the population of the United States is tuberculin-positive. If healing fails to occur there may be general blood infection (miliary tuberculosis) or invasion of a bronchus with rapidly fatal bronchopneumonia.



FIG. 206.—Active Ghon lesion. There is a subpleural caseous lesion in the lower lobe. The lymph nodes at the hilus are enlarged and caseous. Miliary tubercles are scattered through the lung, especially in the lower lobe. Some of the upper lobe has been removed. Death was due to general miliary tuberculosis.

The course of the disease depends on such factors as size of dose and protection against frequent reinfection.

*Epituberculosis* is a clinical term applied to certain tuberculin-positive children who develop a characteristic wedge-shaped x-ray shadow with the base at the pleura and the apex at the hilus that appears suddenly or slowly and then gradually disappears. Although the lesion may be extensive, the symptoms are remarkably mild, and the child may feel perfectly well. The condition is therefore usually discovered accidentally. A similar shadow can be produced experimentally by injecting dead tubercle bacilli into the bronchial tree of an allergic animal; this causes a tuberculous pneumonia which clears by resolution. Human epituberculosis is probably a similar type of mild pneumonitis caused by a caseous node discharging into a bronchus a mass of tuberculo-protein and dead bacilli together with a few viable bacilli.

**B. Reinfection.**—This is usually an infection from without (exogenous), but it is probable that endogenous infection may occur from a primary lesion which has failed to heal. There is a curious immunity between the ages of five and fifteen, and death from pulmonary tuberculosis during these years is extremely rare. The reaction of the now allergic tissues is quite different from that of the primary infection. The right lung is attacked much more often than the left, and the lesion is nearly always just below the apex.

This remarkable apical localization is characteristic of secondary as opposed to primary infection. All sorts of fanciful explanations have been offered, but the most satisfying and that which agrees best with observed facts is the one offered by Dock, which is based on the low pulmonary arterial pressure at the apex owing to the height of the column of blood from the right ventricle to the apex when the patient is erect. It is now known that the pressure at the apex is practically nil when an adult is in the erect posture. In tall, long-chested persons, notoriously susceptible to tuberculosis, the mean pressure will be negative. As a consequence there will be no production of tissue fluid or lymph in the erect posture, immune bodies will not reach the part, removal of oxygen from the alveoli will be minimal, and tubercle bacilli reaching the part will find optimum conditions for growth. Patients with mitral stenosis are almost immune from apical tuberculosis, and in them the pulmonary arterial pressure is sufficiently high to supply the needs of the part. On the other hand the disease is remarkably common in congenital stenosis of the pulmonary valve, a condition which produces the lowest known pulmonary arterial pressure. The higher incidence of right-sided apical lesions can be explained by the fact that the right pulmonary artery is longer and narrower than the left, winds around the aorta, and breaks into lobar branches at some distance before reaching the hilum of the lung. When ulceration or intense peribronchial inflammation occurs there is extensive hyperplasia of the bronchial arterial system with its high systemic blood-pressure, so that conditions become favorable for healing. These considerations explain and emphasize the importance of rest in the

recumbent posture in the treatment of pulmonary tuberculosis. As Dock puts it, "it is the erect posture, maintained for many consecutive hours, which has given man an 'Achilles' heel' through which the acid-fast arrow may pass." In other parts of the lung and in other organs an abundant blood supply under adequate pressure is an essential factor in the acquired immunity of civilized man to the tubercle bacillus.

The result will depend on the size of dose and the degree of resistance. If the dose is small and the resistance high there will be complete healing or a quiet fibrocaseous lesion at the apex. If resistance is not so good there may be rapid excavation, and as the result of cavity formation bronchogenic spread may readily occur. At this stage spread by the lymph stream and blood is comparatively rare, so that lesions in lymph nodes are insignificant. If the dose is large and resistance low there will be a widespread tuberculous caseous pneumonia with fatal termination. If a massive dose is discharged from a caseous gland into the blood stream there will be a general miliary tuberculosis.

The principal distinctions between the primary and secondary infections are the lack of any constant site in the primary form, caseous involvement of the lymph nodes, and the absence of liquefaction and cavity formation.

**1. Healing With Fibrosis.**—This is by far the commonest course for the infection to run, as shown by the nearly constant presence of old tuberculous scars at the apex of one or both lungs in persons who come to autopsy. Just below the apex there is a small depressed pigmented scar which can often be better felt than seen, and is frequently adherent to the chest wall. The black pigment consists of carbon particles contained within phagocytes which have been arrested because of the blockage of the lymphatics by the fibrosis. Lime salts are generally present, and can either be felt or demonstrated in the roentgen-ray film. It may be noted in passing that radiographic evidence of calcified pulmonary nodules may be found in two other types of infection, namely coccidioidomycosis and histoplasmosis. *Microscopically* there may be nothing to see save a pigmented scar (Fig. 207), but sometimes the center may be caseous with a dense zone of fibrous tissue outside. In such a lesion definite tubercles or sometimes merely small collections of lymphocytes may serve to indicate that the infection has not yet died out, as can be proved by animal inoculation, and if the resistance of the patient is lowered by starvation, prolonged exhaustion, influenza, etc., the infection may again awaken into activity. The pathologist will therefore not be misled by the term "healed tubercle."

Whilst healed tuberculosis is the common cause of pulmonary calcification, it is not the only cause. Many persons with pulmonary calcification have a negative tuberculin reaction. In certain areas, particularly in the Mississippi basin, in which histoplasmosis is endemic, large numbers of such persons give a positive reaction to intradermal histoplasmin tests. It is possible, therefore, but by no means proved, that in these regions calcified nodules in the lung may be due to mild

or subclinical infection with *Histoplasma capsulatum*. The specificity of the histoplasmin reaction has still to be verified.

2. **Chronic Fibrocaceous Tuberculosis.**—The characteristic reaction of a body already infected with tuberculosis to an additional heavy dose is breaking-down of the caseous tissue and the formation of a cavity. This is evidence of an allergic condition of the tissues, and is in no way connected with immunity. The softened tissue is discharged into a bronchus and coughed up in the sputum. When the disease has reached this stage it is called "open tuberculosis," and tubercle bacilli are found in the sputum. The bronchial wall is involved in the softening and undergoes dilatation, so that the cavity is formed partly as the result of caseation and softening, partly as the result of bronchiectasis. The first cavities are formed at the apex, and these are always the



FIG. 207.—A healed tuberculous nodule in the lung.

largest, but as the disease progresses other cavities may be formed in the lower lobe. The formation of a cavity is due to the elastic outward pull on an area of softening; this explains its regular outline in the roentgenogram and its comparatively sudden development. The wall of the cavity is smooth, quite unlike the ragged lining of an acute cavity. It may be traversed by bronchi and bloodvessels, and erosion of the latter may lead to serious or even fatal hemorrhage (hemoptysis). In addition to the main areas of caseation and cavitation there are small acinar lesions on the outskirts, composed of yellow caseous acini surrounding a terminal bronchiole. The older these are the more are they fused together into larger masses, the younger and more distant they are the smaller are they likely to be. They are formed by invasion of the terminal bronchioles by tuberculous granulation tissue so that



the corresponding acini collapse and become filled with an exudate which in turn becomes caseous. Just as the acinus is the fundamental unit of lung structure, so the acinar lesions form the fundamental units of the pathology of pulmonary tuberculosis.

So far we have spoken as if the disease were a steadily progressive one, but such is by no means the case. There is fibrosis as well as caseation, and this fibrosis is seen as a thickening of the bronchi, bloodvessels, and pleura, and as numerous white strands on the cut surface. Chronic cavities have a thick and fairly smooth wall. (Fig. 208.) Healing of a cavity may occur; this may take place either by



FIG. 208.—Pulmonary tuberculosis showing cavity formation and fibrosis.

scarring or by the cavity becoming filled with caseous material. A cavity of large size, as seen by *x*-ray, may entirely disappear. Sometimes a cavity may undergo healing in the clinical sense, *i. e.*, it no longer produces sputum filled with tubercle bacilli, and yet remains open, communicating with a bronchus. The caseous lining is shed, the tuberculous granulation tissue becomes fibrosed, and the inner surface of the wall may become epithelialized. A cavity may heal in the pathological sense as the result of occlusion of the draining bronchus, either by obstructive caseous bronchitis, or by the formation of a caseous plug. When the lungs are freed from the normal pull of the

chest by artificial pneumothorax they retract owing to their elasticity, and the cavity shares in this process and tends to collapse and become obliterated. The usual result is a solid nodule due to the retention, inspissation and calcification of the contents of the cavity. Pleural adhesions are very common, especially at the apex, and there may be patches of recent pleurisy. All of this indicates a good defense, and the disease may either remain stationary or may retrogress to a marked degree if the patient receives the best treatment (sanatorium, artificial pneumothorax, etc.). This is the form of tuberculosis which can be treated with such encouraging results, especially in the early stages. The bronchial lymph nodes are either not involved or only to a slight degree. The five chief characteristics of this type of pulmonary tuberculosis are: (1) consolidation and caseation, (2) cavity formation, (3) acinar lesions, (4) fibrosis, (5) relative escape of the tracheo-bronchial lymph nodes, which contain very few bacilli.



FIG. 209.—Pulmonary tuberculosis. Consolidation of the entire lung from caseous pneumonia with acute cavity formation in a boy, aged fifteen years.

The *microscopic picture* varies in different places. The basic lesion is the tubercle, consisting of epithelioid cells and lymphocytes with the usual addition of caseation and giant cells. As the tubercles fuse to form larger masses caseation becomes marked. Much of the elastic tissue remains intact and holds the caseous material together, but when secondary pyogenic infection occurs this tissue is destroyed so that softening soon develops. If the section is stained to show reticulum fibers an abundance will be seen between the cells of the inflammatory exudate, in sharp contrast to what is found in the next form. Proliferation of fibroblasts and fibrosis are very marked, especially in those cases where resistance is good. The arteries may

show an endarteritis obliterans which narrows or even closes the lumen, and this prevents hemorrhage if the wall of the vessel should become ulcerated. The bronchi show inflammatory changes. The surrounding alveoli may contain a cellular exudate, and in the more fibroid forms the alveolar epithelium may become cubical and gland-like.

**3. Acute Tuberculous Caseous Pneumonia.**—This is an acute form of

the disease in which infection overwhelms resistance and sweeps through the lung, so that it gives rise to the clinical picture of galloping consumption or acute phthisis (wasting). The lesions ulcerate through the walls of the bronchi in many places and the infection is widely spread throughout the lung by inhalation. The lesions no longer remain discrete as they tend to do in the previous form, but fuse together to form large caseous areas which may involve the whole of a lobe or even the entire lung and give a pneumonic appearance like that of gray hepatization, so that the condition is called caseous pneumonia. (Fig. 209.) Acute cavities may form in the consolidated tissue, but these are seldom very large, and have the ragged lining characteristic of such cavities with none of the fibrous capsule which shuts off a chronic cavity from the surrounding lung. Pleurisy and bronchitis are present. The tracheobronchial lymph nodes are enlarged and caseous, for the lung is unable to hold back the bacilli which reach the nodes in great numbers.

The *microscopic picture* is one of rapid caseation and destruction with no evidence of resistance on the part of the tissues. The alveoli are filled with an acute cellular exudate, mainly mononuclear in type, which rapidly becomes caseous so that all detail is lost. Elastic tissue is destroyed, and no reticulum fibers are formed between the cells in the alveoli. Neither giant cells nor fibrosis are in evidence. Smears of the exudate and sections of the lung show enormous numbers of tubercle bacilli, far in excess of what is seen in any other form of pulmonary tuberculosis.

**4. Acute Miliary Tuberculosis.**—If a caseous tuberculous focus discharges its contents into a bloodvessel the body is flooded with tubercle bacilli. A caseous bronchial lymph node may become adherent to a branch of the pulmonary artery and open into that vessel, in which case only the affected lung may show the tubercles. More often the vessel is a vein, and then tubercles are found in all the organs as well as in the lungs, the patient often dying of tuberculous meningitis.

The lungs are intensely congested and studded with minute tubercles, many of which can only be seen with the aid of a magnifying glass. At first the lesions are pale and translucent, but as caseation develops they become yellow and opaque. *Microscopically* the tubercles are seen to be everywhere in the fibrous framework of the lung, but the intervening alveoli are either empty or contain catarrhal cells. (Fig. 210.) The tubercles present the usual caseous center, epithelial cells, lymphocytes, and giant cells.

A distinction must be drawn between tuberculous bacillemia and general miliary tuberculosis. A varying degree of bacillemia occurs in every case of tuberculosis; it is by this means that discrete foci in bone, kidney, etc., are set up. But it is only when resistance is overwhelmed that the condition becomes miliary tuberculosis, and it is overwhelmed because of the massive size of the dose, especially if this dose be continually repeated.

Miliary tuberculosis may occasionally be *chronic* and the lesions

may undergo *healing* by fibrosis. What has been called *chronic disseminated tuberculosis* is a condition in which fibrous areas are scattered throughout the lungs; some of these may still show evidence of active infection, whilst in others all such evidence has been lost. The original infection is extrapulmonary in origin, coming probably in small doses from such sites as bones, lymph nodes, and the genito-urinary system. These foci of infection may remain latent for years, and then from time to time give rise to bacillema and metastatic lesions. Emphysema may develop around the fibrous patches, and rupture of the emphysematous bullæ may cause pneumothorax, which is sometimes fatal. A cardinal feature of this form of tuberculosis is the disproportion between the comparatively trifling clinical features and the radiographic evidence of apparently grave disease.

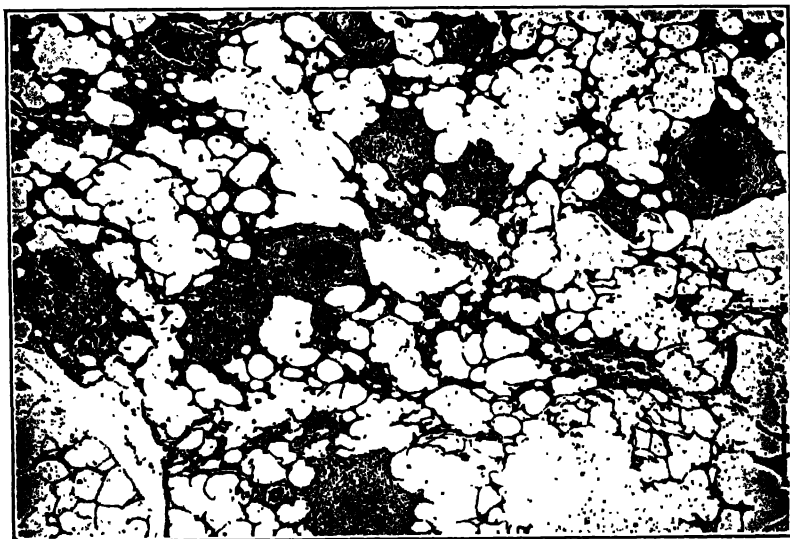


FIG. 210.—Acute miliary tuberculosis of the lung. Between the tubercles the lung tissue is practically normal.  $\times 18$ .

**The Relation of Symptoms to Lesions.**—The *general symptoms* (fever, loss of weight, asthenia, etc.) are due to the absorption of toxins. They become more marked when secondary infection is added to the pure tuberculous infection. *Cough* is a bronchial symptom due to inflammation of the larger bronchi, the walls of which are much more sensitive than those of the bronchioles. *Pain* in the side is due to a tuberculous pleurisy. The character of the *sputum* depends entirely on the form which the lesions take. In miliary tuberculosis there may be no sputum. As long as the lesion remains closed the sputum remains scanty and contains no tubercle bacilli. When cavities form the sputum becomes abundant and purulent and contains numbers of bacilli. It should be remembered that unless the bacilli number 100,000 per cc., of sputum they will probably not be seen with the ordinary Ziehl-Neelsen method. Guinea-pig inoculation is a thousand times more sensitive. The appearance of elastic tissue fibers in the sputum indicates lung destruction. *Hemoptysis* marks the end of the beginning or the beginning of the end. In the early

stages there may be erosion of a small vessel in the process of softening. In the late stages a large artery crossing a chronic cavity may give way causing a severe and possibly a fatal hemorrhage.

The *physical signs* depend on the character of the lesions. The consolidation and cavitation of the fibrocascous form are indicated by dullness on percussion, increased tactile fremitus, and blowing breathing which may become amphoric over a large cavity. All these signs are diminished if the pleura is much thickened. There is not the wooden dullness of lobar pneumonia except in the caseous pneumonic form. Moist râles intensified by coughing (post-tussic) indicate breaking-down of caseous material; they become coarser as the cavities enlarge. A pleural rub may be present in the early stages, but not when extensive adhesions have formed. In the miliary form it will not be possible to detect any evidence of consolidation and auscultatory signs will be absent, but the tiny consolidated areas are easily seen in the roentgen-ray picture. Small calcified lesions, Ghon lesions, and, of course, more extensive consolidation and cavity formation are clearly shown by the roentgen-rays.

Complications such as empyema, pneumothorax due to the rupture of a subpleural cavity, and tuberculosis of the larynx need only be mentioned here, as they are considered elsewhere.

**Broncholithiasis.**—Known also as bronchial calculus and lung stone, this term signifies the presence of calculi in a bronchus. The usual origin is a caseous tuberculous focus in the lung or lymph nodes or the inspissated pus of an old lung abscess. The calculus erodes through the bronchial wall, or it may be formed within the lumen of the bronchus. The calculi, which are often multiple, are hard and irregular. They may be expectorated, or may remain within the bronchial lumen and cause obstruction.

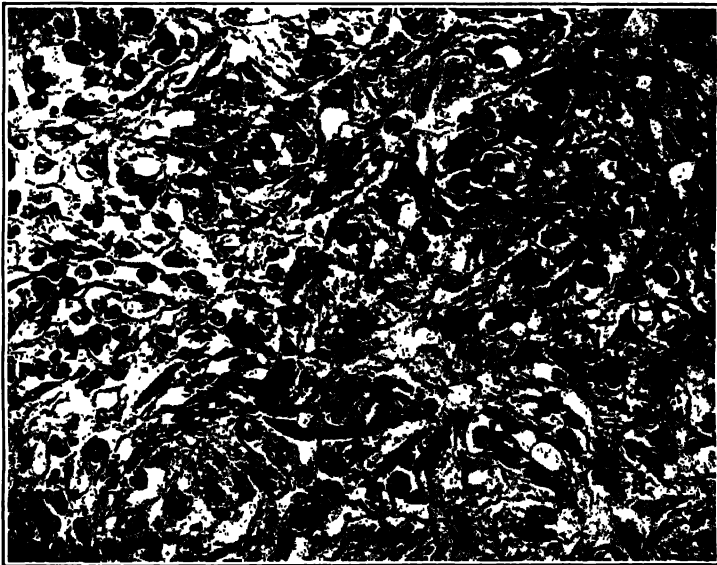


FIG. 211.—Congenital syphilis of the lung.  $\times 300$ .

### SYPHILIS OF THE LUNG

Syphilis of the lung may be congenital or acquired. The former is much commoner and much more characteristic than the latter.

The *congenital form* is seen in syphilitic infants. The child is either born

dead or dies in a few days. The lung or part of it is consolidated so that it sinks in water, and is of a pale gray color. For this reason the condition is called *pneumonia alba*. It is an interstitial pneumonia caused by enormous number of spirochetes scattered through the lung, with the formation of a large amount of cellular fibrous tissue. (Fig. 211.) The alveoli are small, separated by the fibrous tissue, and lined by cubical epithelium so as to have a gland-like appearance. The picture is one of arrested development rather than active inflammation. I have seen nodular lesions, like gummata in the gross.

The *acquired form* is very uncommon, although the clinician often makes the diagnosis on a combination of a positive Wassermann test and roentgen-ray shadows. The lesions may take one of three forms. (1) *Ulceration of a bronchus* with subsequent stenosis is probably the commonest and the most clearly defined of the lesions. There may be severe hemoptysis owing to erosion of a vessel. When healing occurs the mucous surface may be scarred like a rope-ladder, and contraction of the scar tissue will lead to narrowing of the bronchus and collapse of one or more lobes of the lung. (2) *Gummata* may be scattered through the lung. They heal with scarring, but it is very difficult to be certain if old scars in the lung are syphilitic. (3) A *diffuse fibrosis* is the most difficult form for the pathologist as well as the clinician to diagnose. The usual non-pathognomonic histological picture of syphilis is reproduced.

### MYCOTIC INFECTIONS OF THE LUNG

Mycotic diseases of the lung due to the higher fungi are easily confused with tuberculosis even in the autopsy room, for caseation and cavity formation are among the chief features. The only certain method of distinction is the finding of the organisms in the tissue.

**Blastomycosis.**—This is probably the commonest of the pulmonary mycoses. The spores may be inhaled directly, or infection may spread by the blood stream from skin lesions to the lung. The lesions (consolidation and cavitation) are very much like those of tuberculosis, but there is more suppuration and giant-cell formation. The blastomycetes are seen in the microscopic sections in large numbers and also in the sputum and pus. The prognosis is far worse than in tuberculosis.

**Actinomycosis.**—The actinomyces are inhaled into the lung or spread from the mouth. They never spread by the blood stream. The lesions are like those of fibrocascous tuberculosis, but instead of cavitation there is abscess formation. Moreover the lower lobe is most often involved. As usual the disease spreads by contiguity, not by the lymph or blood stream, so that it extends to the chest wall, spine, and through the diaphragm, forming numerous sinuses, but not involving the bronchial lymph nodes or distant organs. The fungus is found in the "sulphur granules" in the pus and sputum. The disease is usually fatal in from six months to a year.

**Streptothricosis.**—A rare infection by a branching fungus. The pulmonary lesions are of the septic type—abscess, gangrene and bronchiectasis. The infection may spread by the blood stream to the brain and elsewhere.

**Aspergillosis.**—This is caused by *Aspergillus fumigatus*, a filamentous fungus with a basal stem and a stalk supporting a spore-bearing head. The disease occurs amongst bird fanciers, pigeon stuffers, and other grain handlers. The lesions are similar to those of tuberculosis, with necrosis and cavitation. Mats of mycelial threads may be seen in some areas. The x-ray picture may suggest miliary tuberculosis or silicosis.

**Coccidioidomycosis.**—This condition is discussed on page 187.

### CIRCULATION DISTURBANCES OF THE LUNG

**Active Congestion.**—This is rather an ill-defined condition which may be the result of irritating gases or the initial stage of an acute

inflammation. The vessels in the alveolar walls are distended with blood.

**Passive Congestion.**—In passive congestion the dilatation of the vessels is a passive affair due to mechanical causes. Two forms are recognized: (1) brown induration, a chronic process, (2) hypostatic congestion, usually a terminal one.

**Brown Induration.**—This is due to some central obstruction to the circulation, and is best seen in mitral stenosis, the blood accumulating in the lung. The lungs are voluminous, russet-brown in color, tough, and indurated (brown induration). *Microscopically* the lung is filled with blood, the alveolar vessels being widely distended, and the alveoli containing many red blood cells. The characteristic feature is the presence of great numbers of large phagocytic cells filled with yellow pigment. These cells are known as *heart failure cells* even when they occur in other than cardiac conditions, and are probably derived from the histiocytes (reticulo-endothelial cells) of the alveolar walls, not from the pulmonary epithelium as is supposed by some. The pigment is hemosiderin, derived from the red blood cells in the alveoli, and gives the Prussian blue reaction for iron. There is also a marked increase in the connective tissue of the lung, which is partly responsible for the toughness and induration. The alveolar walls are thickened, so that the vascular endothelium is separated from the air in the alveoli. This interferes with oxygenation of the blood, and is responsible for some of the dyspnea of mitral stenosis. Hemoptysis is a common symptom of mitral stenosis, and is due to the hemorrhage into the alveoli.

**Hypostatic Congestion.**—An accumulation of blood in the lower and posterior part of the lung is found at every autopsy, and is due to relaxation of the vessels after death plus the force of gravity. A much more advanced condition is found in patients with some debilitating illness and weak heart's action who have been kept on their back. The dependent part of the lung may appear to be consolidated, so that without the microscope it may be impossible to tell if the condition is hypostatic congestion or hypostatic pneumonia. The air in the alveoli is replaced by plasma and red blood cells, but a pneumonic process may be added as the result of terminal infection.

**Edema.**—A slight degree of pulmonary edema is almost as common as congestion and may be seen at the base of the lung in nearly every autopsy. It is due to failure of the heart as the patient is dying. Pronounced edema may take two main forms, inflammatory and mechanical.

**Inflammatory Edema.**—This forms a part of any inflammatory exudate, the plasma readily passing from the vessels into the lumen of the alveoli. The amount varies depending on the irritant. It is very abundant in influenzal pneumonia, where the lung becomes water-logged. A varying amount of the plasma is converted into fibrin, the proportion being extremely large in pneumococcal pneumonia. The increased capillary permeability characteristic of shock

results in edema. Many cases of so-called terminal edema are of this nature.

**Mechanical Edema.**—This variety is due to chronic heart failure. The edema is due, as Welch showed in experimental work on animals, to a disproportion between the working power of the two ventricles. If the left ventricle fails more rapidly than the right, the pulmonary vessels become distended and plasma leaks through the capillary walls into the alveoli. If we ask *why* the fluid leaks through, we find ourselves confronted with the difficult problem of edema which has already been discussed in Chapter III.

Pulmonary edema of the mechanical type is naturally a chronic condition. An *acute pulmonary edema* may occasionally develop, for which no adequate cause can be found at autopsy. The patient usually has chronic nephritis or high blood-pressure, and it appears as if some sudden strain had been thrown on the left side of the heart. An acute and fatal pulmonary edema may follow a surgical operation; I have seen this accident occur in a simple appendectomy. In rare cases acute edema of the lung may come on after removal of a pleural effusion. Here the lung which has been compressed for a long time suddenly expands, and for some reason fluid pours from the vessels into the alveoli.

The *gross appearance* of the lung is characteristic. It is voluminous, heavy, firm, or doughy, and shows marked pitting on pressure. In the mechanical variety the edema is most marked in the dependent parts of the lung (base and posterior border). The consolidation may be so marked as to simulate pneumonia, but steady pressure will force the fluid out and leave the lung soft. When the lung is cut and squeezed, water pours from the cut surface and from the bronchi. If the condition is very marked as in influenzal pneumonia or acute edema of the lung the fluid pours out of the water-logged organ without any pressure being used. The color of the fluid depends on the presence or absence of congestion. If this is marked the fluid is bloody, if absent the fluid is clear and watery.

The *microscopic picture* is that of alveoli filled with fluid coagulated by the fixative. (Fig. 212.) The more albuminous the fluid, the more intensely does it stain with eosin. If the fluid has a very low protein content (mechanical edema), it may tend to be washed out by the fixative. In such cases the edema is best demonstrated by fixing the tissue for a few moments in boiling formalin which coagulates the fluid *in situ*. The material which fills the alveoli appears as a hyaline sheet, but sometimes it is granular. In inflammatory edema there may be a varying amount of fibrin formation.

**Embolism and Infarction.**—This subject is fully discussed in connection with the general question of embolism in Chapter III. The thrombosis which precedes the embolism is often postoperative, especially after operations on the female pelvis, but the condition is even more frequent in purely medical (chiefly cardiac) cases. The first embolus may prove fatal. As a rule, however, a fatal embolus is



preceded by a number of smaller emboli which can be detected clinically and recognized as danger signals. In this case the use of anticoagulants such as heparin and dicumarol can arrest the formation of thrombi in the veins and thus protect the patient against fatal embolism. In practice this procedure has proved extremely valuable. Ligation of the veins in the leg has a similar effect. If the embolus is large and blocks a main artery death may occur in the course of a few minutes from shock. In this case there is no time for an infarct to be produced. When the embolus is smaller a red infarct is formed with hemorrhage into the alveoli, hemoptysis, and pain in the side due to a patch of pleurisy over the infarct. When the infarct is larger there may be a hemorrhagic pleural effusion. As recovery takes place the infarct is partly absorbed, partly replaced by a scar which can seldom be detected if the patient dies later. If, however, formalin is instilled into the trachea and the lungs are then inflated to their original size, healed infarcts can often be demonstrated. Chronic pleuritis and puckering are easily mistaken for healed tuberculosis. Persistence of elastic tissue and the demonstration of an organized embolus help to distinguish a healed infarct from tuberculosis. Further details will be found in Chapter III.



FIG. 212.—Edema of the lung. The acini are filled with albuminous fluid.  $\times 150$ .

**Fat Embolism.**—As a result of fracture, crushing injuries, and traumatic lesions of fat, globules of fat may enter the torn veins and be carried to the lungs. Here they seldom do much damage, but if present in very large amount there may be dyspnea and prostration. The gross appearance of the lung is normal, but in frozen sections stained for fat, globules and cylinders are seen in the capillaries. If the fat passes through the lung it may reach the kidneys and be excreted, or it may lodge in the brain with fatal results.

## ATELECTASIS

Atelectasis literally means incomplete expansion (*ateles*, incomplete + *ektasis*, expansion), but it is now synonymous with collapse of the lung. This may be: (1) congenital, (2) compression, or (3) obstructive.

**Congenital Atelectasis.**—This is the only form of collapse which deserves to be called atelectasis, for the alveoli have failed to expand. It is seen in the stillborn child who has never breathed, and in children who live only a few days and never breathe well, the lung shows many areas of atelectasis. The lung is dark, firm, and airless. If only a part is collapsed, that area is depressed below the surrounding surface.

The collapsed lung sinks in water, a convenient practical test to determine if the child has breathed. The lung may have to be cut into separate pieces, for a small part may have become expanded. It is commonly stated that the alveolar epithelium of the full term fetus is cuboidal in form, giving the alveoli a gland-like appearance. This is not correct. It is true for the earlier stages of development, but after the fifth month the cuboidal epithelium begins to disappear and the alveoli to be opened up. The difference between the lung which has inhaled air and the one which has not is quantitative rather than qualitative. As the result of extra-uterine respiration the alveoli are more fully distended and their walls are thinner than if the child has never breathed. If the body has been kept for some time in a warm room the lung may float due to the production of gas by putrefying bacteria. In such cases bubble-like areas are seen microscopically in the septa and alveoli; these are easily distinguished from alveoli partially distended as the result of intra-uterine respiration.

**Compression Atelectasis.**—Pressure on the lung drives out the air and produces collapse. This may be *complete* when the pressure is great and uniform as in massive pleural effusion, empyema, and pneumothorax, but only *partial* when the pressure is more local as in pressure by a tumor, an enlarged heart, or an elevated diaphragm. When the pressure is removed the lung will expand again, but lesions may be formed (as in empyema) which may prevent re-expansion.

**Obstructive Atelectasis.**—In this form two factors are nearly always at work, obstruction of a bronchus and weakening of the respiratory movements (chest or diaphragm). If obstruction is due to a foreign body in a bronchus the second factor will not be present, but usually it is caused by an accumulation of mucus in the bronchioles associated with poor respiratory movements. If deep breathing and coughing were possible the obstruction in the bronchioles would be cleared away. This type of atelectasis is commonest in debilitated children suffering from bronchitis, bronchopneumonia, etc. Indeed in such children even the normal amount of mucus in the bronchioles may lead to partial collapse. The two factors are present after an abdominal operation, for the anesthetic will stimulate the bronchial secretion, and the abdominal section will prevent the patient from breathing deeply. In all of these instances the air in the affected part of the lung is absorbed into the blood, no more air can enter on account of the obstruction, and that part of the lung collapses.

**Acute Massive Collapse.**—This peculiar and rare complication is a special example of obstructive atelectasis caused by the two factors, bronchial obstruction and respiratory weakness. The clinical picture is a striking one. From a few hours to a few days after an operation, usually abdominal, the patient suddenly develops the symptoms of an acute thoracic catastrophe, *i. e.*, extreme dyspnea, marked cyanosis, and collapse. There is no respiratory movement on the affected side, the heart is displaced to that side, there are physical signs of consolidation of the lung, and the roentgen-rays show a peculiarly dense shadow

and the dome of the diaphragm high and immobile on the side of the collapse.

Massive collapse may occur in a confusing variety of conditions, *e. g.*, after abdominal operations, as the result of severe wounds (non-penetrating wounds of the chest, wounds of the abdomen, pelvis, legs), and as a complication of diphtheria. As a result of these conditions the patient's respiratory movements are weakened (from shock of wounds, etc.), and secretion collects in the bronchial passages, especially in diphtheria. Chevalier Jackson has shown that the symptoms and roentgen-ray picture in cases of bronchial obstruction by a foreign body may be identical with those of acute massive collapse, and that when the diphtheritic membrane is removed by means of the bronchoscope the symptoms rapidly clear up. The cough reflex is the watchdog of the lungs, and when this is interfered with on account of debility, abdominal pain, shock, etc., plugs of mucus may accumulate in the bronchi and give rise to massive collapse. It must be admitted that we need more light on the sudden production of such an extensive lesion, and it is possible that the above explanation may prove to be quite wrong.



FIG. 213.—Atelectasis.  $\times 225$ .

**Morbid Anatomy.**—The condition of the lung is similar in all forms of atelectasis, whether congenital, acquired, or massive. In the massive form and in compression due to pleural effusion or pneumothorax the entire lung may be so collapsed that it no longer fills the cavity but lies against the posterior chest wall and vertebral column like a squeezed sponge. If only some parts are affected, these are firm, inelastic, airless, and sunk below the surrounding surface. These areas are steel-blue or slate-gray due to stasis of the circulation.

*Microscopically* the alveolar walls are pressed together so that the lumen is nearly obliterated. (Fig. 213.) In the congenital form the fetal structure is still evident. If the collapse is of long duration fibrosis may occur which will prevent full expansion.

## EMPHYSEMA

Emphysema is the opposite of atelectasis. The word means inflation, and the alveoli are distended instead of collapsed and their walls are atrophic. Emphysema is usually general and affects both lungs.

It is a complication of diseases in which there is much coughing or violent expiratory efforts. It usually comes on slowly as the result of chronic bronchitis, pulmonary tuberculosis, etc. Sometimes it is more acute in onset following whooping cough or bronchial asthma. It is said that the playing of wind instruments is a causal factor, but this is probably a myth. If the patient plays in a band he is as likely to perform on the big drum as on the trombone. The local form is probably compensatory in nature, being found in the neighborhood of areas of consolidation and collapse.

**Morbid Anatomy.**—The lungs are very voluminous, very pale, and quite dry. The heart may be completely covered, so that there is no cardiac dulness on percussion. Large blebs or bullæ project on the

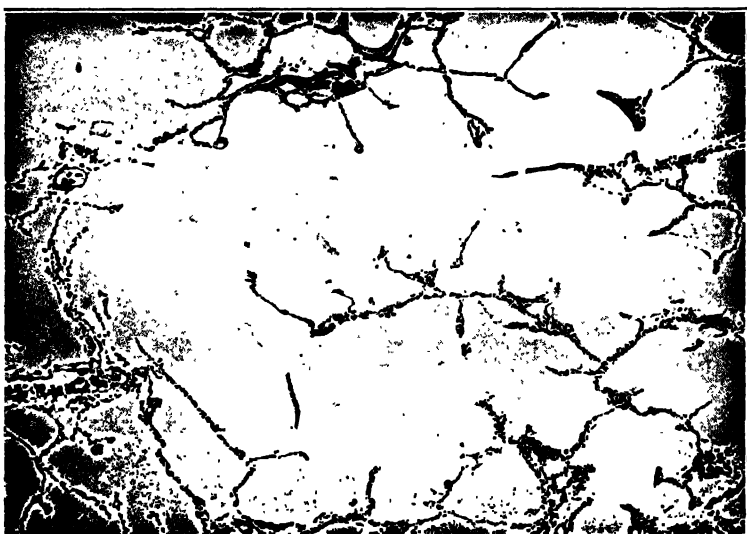


FIG. 214.—Emphysema of lung. Great dilatation of alveoli with breaking down of alveolar walls.  $\times 60$ .

surface in the more poorly supported regions (apex, anterior margin, base). The lung has a peculiarly soft, dry, feathery feel. There is marked pitting on pressure due, not to edema, but to destruction of the elastic tissue. *Microscopically* the lung presents a delicate lace-like structure. The air vesicles are few in number and of great size, the septa between many of the adjacent alveoli being broken down. (Fig. 214.) The consequent loss of elastic tissue explains the pitting on pressure. In the remaining septa the vessels are greatly narrowed if not obliterated. It is this avascularity which is responsible for the pallor of the lung and the dryness of the cut surface. It causes serious obstruction to the pulmonary circulation. The distention of the alveoli and destruction of the alveolar walls is due to the increased intra-alveolar pressure during coughing, asthmatic attacks, etc.

**Effects.**—The effects of emphysema are far-reaching and serious. The chest has a barrel-shaped appearance, the ribs being raised and the sternum pushed forward, so that the antero-posterior equals the transverse diameter. The costal cartilages are calcified so that the thorax is fixed in an expanded condition. The lungs are hyper-resonant, and the area of superficial cardiac dulness obliterated. Respiratory movements are diminished, and expiration is difficult and prolonged. Owing to the vascular occlusion there is marked obstruction in the pulmonary circulation, so that there is great hypertrophy and dilatation of the right ventricle and general venous congestion throughout the body. The pulmonary artery may show arteriosclerosis, just as it does in the obstruction due to mitral stenosis. Dyspnea and cyanosis develop, with a compensatory increase in the number and size of the red blood corpuscles. One of the emphysematous bullæ may rupture into the pleural cavity, giving rise to spontaneous pneumothorax.

**Atrophic Emphysema.**—This condition is seen in old age (senile emphysema) and in wasting diseases. It is not a true emphysema, for there is no distention of the alveoli, no enlargement of the lungs, no bullæ on the surface. The only resemblance lies in the microscopic picture, where there is atrophy and disappearance of the walls of the alveoli so that large spaces are formed. The condition is an atrophy from defective nutrition, and does not deserve to be called emphysema.

**Interstitial Emphysema.**—This also is not a true emphysema. The air escapes from the alveoli and makes its way into the interstitial tissue of the lung, particularly along the perivascular sheaths, as a result of which there may be serious pressure on the vessels. This is usually due to tearing of the lung by a fractured rib, wound, etc., but in children it is sometimes caused by over-distention and rupture of the alveoli during the violent paroxysms of whooping cough. The air collects in the lymphatics in the form of tiny beads, which are best seen under the pleura. It may then pass to the mediastinum and from there to the neck and down over the chest wall. The lung and the subcutaneous tissues have a peculiar and quite characteristic crackling feel.

## TUMORS OF THE LUNG

**Carcinoma.**—Primary cancer of the lung used to be regarded as a rarity, but during the last twenty-five years it has become remarkably common. Indeed it has been said that "it is important to think of a pulmonary neoplasm when a patient in the cancer age, showing no symptoms of cardiac, renal or arterial disease, begins to cough and is short-winded." There has been much discussion as to whether this increase is real or only apparent, and if real, what has caused it. There is no doubt that the number of reported cases has increased enormously in recent years, but it appears to me unlikely that there is any real increase in the incidence. Goethe once remarked "Was man weiss, sieht man," and particularly in connection with the diagnosis of cancer of the lung is it true that what one knows, one sees. The physician sees bronchogenic carcinoma because he is thinking about it. The surgeon thinks about it when he sees enlarged supraclavicular lymph nodes. It is continually in the radiologist's mind in any obscure chest case, although all he may detect is atelectasis or persistent pleural

effusion. The pathologist realizes: (1) that the diagnosis formerly frequently made of mediastinal lymphosarcoma or mediastinal tumor has now to be changed to bronchogenic carcinoma; (2) that the tumor may be anaplastic like a sarcoma, adenocarcinomatous suggesting glandular origin, or epidermoid suggesting a skin tumor; (3) that the natural history of the tumor (metastases to liver, adrenal, kidney, bones and brain) is extremely suggestive of a primary pulmonary neoplasm; (4) that many cancers of the lung have in the past been mistaken for secondaries, the supposed primary being in one of the above-mentioned organs; (5) that a bronchial cancer may be represented merely by a roughening of the mucosa or a narrowing of the lumen and therefore may very readily be missed; and (6) that secondary changes such as abscess formation may obscure the true nature of the lesion to such an extent that cancer is not even suspected. There is little change in the total incidence of intrathoracic growths. Steiner in an analysis of the material examined in the department of pathology of the University of Chicago during the forty-year period between 1902 and 1941 came to the conclusion that there was no real increase in the frequency of bronchogenic carcinoma.

**Etiology.**—The literature is full of etiological factors, most of which are purely fantastic. Only three need be mentioned: tuberculosis, influenza, and the inhalation of irritating substances. I do not believe that the first two are of any importance. It seems likely that the inhalation of an irritant may play a part, but we have no idea of the nature of this irritant. The waste products of automobiles and the tarring of roads have been blamed, but most of my cases in Winnipeg were from the prairies where automobiles are not numerous and tarring is unknown. Cases have been reported in persons exposed to chemical fumes. It has been suggested that silicosis may cause the disease, but the evidence is not conclusive.

The most interesting etiological facts are those relating to the Schneeberg lung cancer. For centuries there has been a very heavy incidence of cancer of the lung in workers in the cobalt mines in Schneeberg in Saxony, although no cases occurred in persons living in the same district but not working in the mines. Here some irritant is evidently at work, but the nature of that irritant is still undetermined. The Schneeberg miners are exposed to *mechanical* irritation from stone dust, to *chemical* irritation from a dust rich in arsenic and other irritants, and to a *radio-active* emanation in the air. A recent example of the same kind of thing is seen in the Joachimsthal lung cancer, occurring in workers in pitchblende (radium) mines in Joachimsthal in Bohemia, which are only 20 miles from Schneeberg. In Joachimsthal 90 per cent of all malignant tumors occur in the lung. In conclusion, it should be noted that the disease is very much commoner in the male.

**Symptoms.**—The chief symptoms are cough, blood-stained sputum, dyspnea, and pain in the chest. These symptoms are due partly to pressure, partly to bronchial obstruction. There may be pressure on any of the structures in

## PLATE X



### Bronchogenic Carcinoma

The carcinoma is arising from and occluding one of the main bronchi. The corresponding part of the lung and the pleura are infiltrated with tumor.





the chest. Pleural effusion occurs in about 50 per cent of the cases and is often blood-stained. Fever and leucocytosis are occasional symptoms which tend to confuse the diagnosis. The diaphragm on the affected side is drawn up to a remarkable degree (tenting of the diaphragm) as seen in the roentgen-ray film. The film often fails to indicate any tumor, merely showing such effects of the tumor as atelectasis, pleural effusion, enlarged mediastinal glands, etc. In secondary carcinoma, on the other hand, the tumor itself can be readily seen. Although the patient is usually in the cancer age, I have seen a number of cases under twenty-five years of age. Bronchoscopic examination is of great value; it may show a definite tumor, mucosal roughening, stenosis, or merely interference with the normal movements. It may be possible to obtain a fragment of tumor for biopsy through the bronchoscope. The breath sounds are remarkably absent over the affected area, even though the bronchi may not be correspondingly narrowed on bronchoscopic examination. Tumor cells may be found in the sputum examined by the wet-film method (smear fixed wet in corrosive sublimate).

**Lesions.**—Carcinoma of the lung is essentially bronchogenic in origin. (Fig. 215.) The gross appearance varies to an extraordinary degree, which is one of the reasons why in the past the correct diagnosis has been so often missed in the autopsy room. The most common finding is a firm grayish-white tumor in the region of the hilus showing more or less evident relation to a main bronchus. It may project into the lumen as a papillary mass which may block the bronchus and cause atelectasis. (Plate X.) The nature of such a lesion is self-evident. But it may merely cause a white fibrous thickening of the bronchial wall with narrowing of the lumen and only a suggestion of roughening of the mucosa. If one is not familiar with the existence of this type of lesion the diagnosis will probably be missed. Not rarely a microscopic examination of the suspected lesion is necessary before a definite report can be given. The size of the tumor varies greatly. It may be no more than 1 to 2 cm. in diameter and yet may have caused large and multiple metastases responsible for the death of the patient. Usually, however, it extends outward for a considerable distance into the surrounding lung, and may fuse with the enlarged bronchial lymph nodes. (Fig. 216.) In a relatively small number of cases the tumor arises in the peripheral part of the lung from a small bronchus; such tumors tend to be more circumscribed, and are those best suited for



FIG. 215.—Origin of bronchogenic carcinoma from bronchial epithelium.  $\times 75$ .

surgical removal. The rest of the lung may show a few or many smaller nodules, representing spread along the lymphatics.

Secondary changes may greatly alter the gross appearance. These changes are atelectasis, bronchiectasis and abscess formation. If a main bronchus is blocked a lobe or the entire lung may be completely collapsed. Massive pleural effusion often blood-stained may add to the collapse. A lobe or a lung may be riddled with bronchiectatic cavities, which may develop into abscesses. Sometimes the tumor itself is so completely destroyed by the abscess that microscopic examination is necessary to detect its presence.



FIG. 216.—Primary carcinoma of the lung. Part of the new growth is the lung tumor, but part is the greatly enlarged bronchial lymph nodes.

Two other forms are described, but are of little importance. The first is a *miliary type*, in which tiny nodules are scattered through the lung; at least the majority of these cases are secondary to an undiscovered primary focus. The second is a *diffuse type* which resembles *pneumonia*.

The *microscopic appearance* is most varied. There is perhaps no tumor which is so pleomorphic as cancer of the lung, and this explains why in the past it has been so frequently mistaken for other tumors. The cells vary from the most undifferentiated or anaplastic to the most fully differentiated. The anaplastic cells may be small round cells of the simplest type (Fig. 220) or spindle-shaped like those of a spindle-cell sarcoma. They may be oval, as in the "oat-cell" type of English writers. All of these have commonly been regarded as sarcomas (round-cell, spindle-cell, oat-cell) in the past. The more

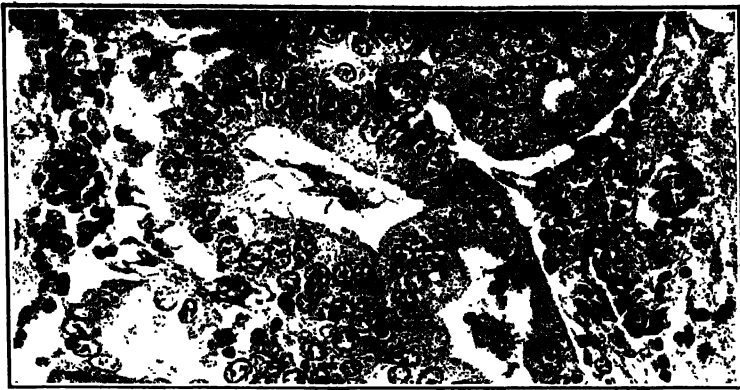


FIG. 217

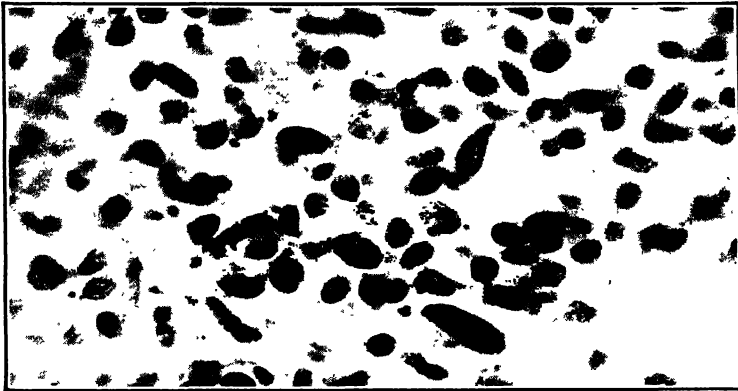


FIG. 218

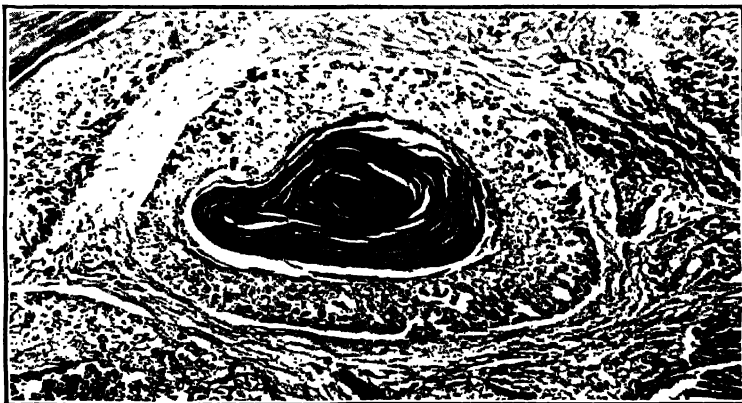


FIG. 219

FIGS. 217, 218 and 219.—Bronchial Carcinoma. FIG. 217.—Adenocarcinoma.  $\times 325$ .  
 FIG. 218.—Anaplastic.  $\times 700$ . FIG. 219.—Epidermoid.  $\times 150$ .

differentiated cells are cubical or columnar in shape, and may be collected in groups (medullary arrangement) or arranged around gland-like spaces into which papillary processes may project (adenocarcinomatous arrangement). Sometimes the tumor cells seem to have crept along inside the alveolar walls and formed a new lining for the alveoli. Such an appearance has been considered by some workers to represent a separate type which they designate as alveolar cell carcinoma in the belief that the tumor arises from the cells lining the alveoli. It is much more probable that they are of bronchial origin, or, as is usually the case, secondary adenocarcinoma from some discovered or undiscovered focus in another organ (Herbut). Finally the differentiated cells may be of the squamous type. (Fig. 221.) As the

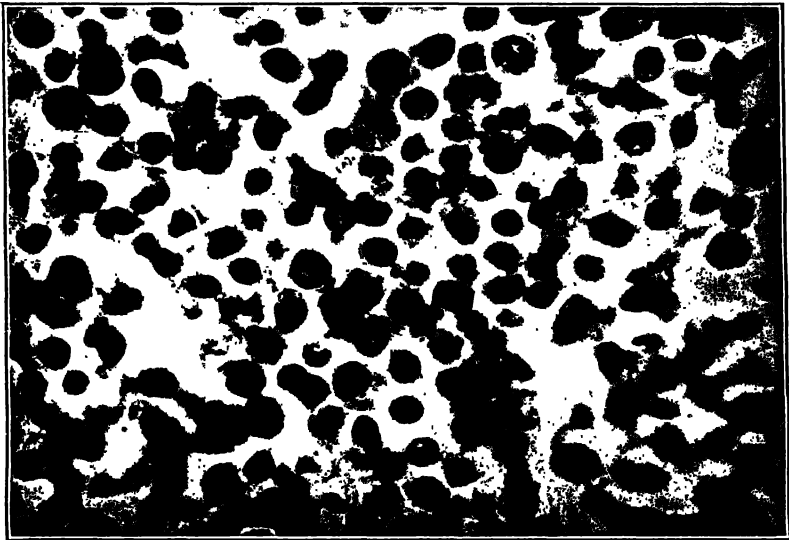


FIG. 220.—Primary carcinoma of lung of anaplastic type. Easily mistaken for a round-cell sarcoma.  $\times 700$ .

bronchial epithelium is capable of differentiating in various directions, there is no reason to suppose, as has been suggested, that this type arises from the cells lining a bronchiectatic cavity which have undergone metaplasia.

Carcinoma of the lung may therefore be divided into three histological groups: (1) small cell or anaplastic, (Fig. 218); (2) epidermoid or squamous cell, (Fig. 219); and (3) glandular. (Fig. 217.) Of these, the first two are the most common. The small cell carcinoma occurs at an earlier age, spreads widely throughout the lymphatic system and by the blood stream, and runs a rapid course. The adenocarcinoma also spreads extensively. The epidermoid type is the most favorable for surgical operation, for the tumor remains confined to the hilus for some time, involvement of lymph nodes is not marked nor does it

occur early, and there is little tendency to metastasize by the blood stream, spread being local rather than to a distance. Mucin is usually present in the adenocarcinomas. It is highly suggestive of cancer of the lung, but does not prove an origin from the mucous glands. The stroma



FIG. 221. — Bronchogenic carcinoma. The oval cells are very characteristic.  $\times 700$ .

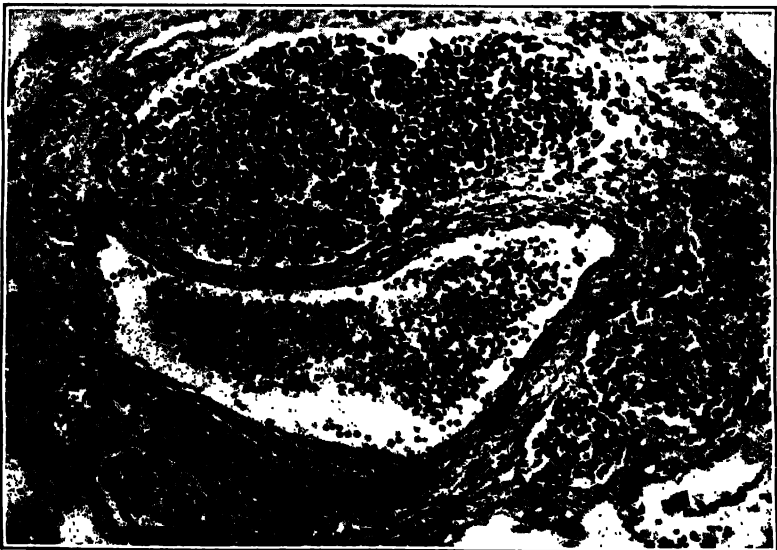


FIG. 222.—Dilated perivascular lymphatics filled with tumor cells. The lumen of the vessel contains red cells.  $\times 175$ .

is very variable. It may be very scanty or so abundant as to suggest scirrhus cancer of the breast. Silver staining shows that the connective-tissue reticulum separates clumps of tumor cells, but does not penetrate between even the most anaplastic cells, thus indicating that these tumors are true carcinomas, however closely they may resemble sarcomas.

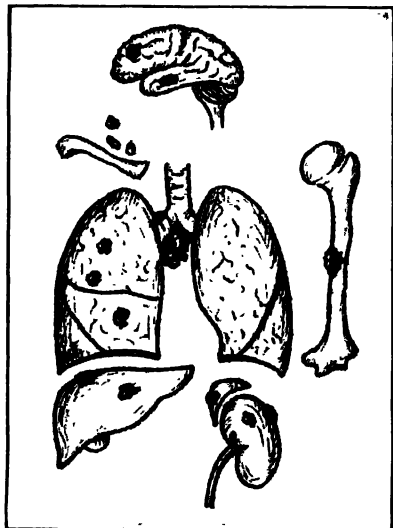


FIG. 223.—Diagram to illustrate sites of metastases in bronchogenic carcinoma.



FIG. 224.—Adenoma of bronchus.  $\times 275$ .

**Spread.**—The tumor tends to spread far and wide and the secondary growths may be the first announcement that there is anything wrong with the patient. Spread is three-fold: (1) through the lung, (2) to the lymph nodes, and (3) to distant organs. *Spread through the lung* is mainly by way of the perivascular and peribronchial lymphatics with the formation of new nodules at a distance from the primary tumor. (Fig. 222.) The tumor cells may also creep along the bronchioles and form a new lining for the alveoli. There may be extension to neighboring structures (pericardium, heart, etc.).

*Spread to the lymph nodes* is constant; first the regional nodes (tracheobronchial and mediastinal), but later more distant glands (supraclavicular, cervical, and retroperitoneal) may be involved. The mediastinal mass may be larger than that in the lung, and in the past a diagnosis has often been made of mediastinal sarcoma with secondary growth in the lung.

*Spread to distant organs* is very common. The order of frequency is as follows: (1) liver, (2) brain and bone, (3) kidney and adrenal. (Fig. 223.) Less commonly the pancreas, thyroid, etc., may be involved. The combination of metastases in brain and adrenal is remarkably common. In my material half the cases of all secondary tumors of the adrenal were due to bronchogenic carcinoma. The brain

metastasis is often mistaken clinically for a primary cerebral tumor, because the cerebral symptoms may precede the pulmonary ones.

**The Relation of Symptoms to Lesions.**—The symptoms are due to pressure and obstruction. The persistent *cough* is due to irritation of a bronchus by the growth. *Bloody sputum* or actual hemorrhage is caused by ulceration of the bronchial mucosa. Occlusion of the bronchus leads to *atelectasis* with displacement of the heart and limitation of movement on the affected side. *Dyspnea* is a common and marked symptom and is probably due to *partial* blocking of a main bronchus, thus interfering with the ventilation (aeration) of a lobe or an entire lung. If the obstruction is complete and the other bronchi are patent there is no dyspnea because the lobe or lung is completely collapsed, there is no partial circulation through it, so that the aerated blood is not polluted by impure blood from the obstructed portions. This is also true of *cyanosis*, although not to the same extent. *Pain* in the chest or back may be due to pleurisy, pressure on nerves, or metastases in the vertebral column. *Pleural effusion* is common and is due to carcinomatous involvement of the pleura. The fluid is often blood-stained, reaccumulates rapidly after removal, and may contain clumps of tumor cells. There may be *pressure* on the esophagus, trachea, and recurrent laryngeal nerve with corresponding symptoms. *Fever* and *leucocytosis* may be due to occlusion of a bronchus and the accumulation of purulent material in the resulting bronchiectatic cavity.

**Adenoma of Bronchus.**—This rather uncommon tumor is remarkable for its long duration punctuated by repeated hemorrhages. Thus in a case of mine there were hemorrhages, sometimes copious, over a period of twenty-five years. The tumor is usually an adenomatous polyp growing in a main bronchus and causing obstruction of the lumen as well as hemorrhage. It forms a striking object when seen with the bronchoscope. Microscopically it consists of epithelial cells strikingly uniform in type and arranged around acini, but sometimes forming solid masses. (Fig. 224.) Although the tumor is benign there is distinct invasion of the surrounding parenchyma and sometimes of the lymphatics. An adenoma may become carcinomatous, so that lobectomy is preferable to removal through the bronchoscope. It has been suggested that these tumors arise from embryonic bronchial buds which fail to develop and that they should be classed as "mixed tumors," similar to those which occur in the salivary glands (Womack and Graham).

**Sarcoma.**—Primary sarcoma of the lung is very rare, although many supposed cases have been described. The great majority of these have undoubtedly been examples of the anaplastic form of carcinoma, in which the cells may be round, spindle- or oat-shaped. Examination of a number of blocks of tissue will usually give some hint (medullary arrangement, etc.), that the tumor is carcinomatous, and the method of spread (lymph node involvement, etc.), serves to confirm this opinion.

**Hemangioma.** This is a rare tumor of the lung. It is really an arteriovenous fistula, an abnormal communication between arteries and veins. It can be diagnosed clinically and removed by operation, the chief features being increased blood volume, cyanosis, polycythemia and clubbing of the fingers and toes.

**Superior Pulmonary Sulcus Tumor.**—There is a clinical syndrome characterized by pain about the shoulder and down the arm, Horner's syndrome, local destruction of the first two or three ribs, atrophy of the muscles of the hand, and a roentgen-ray shadow at the extreme apex. Pancoast suggested the name of superior pulmonary sulcus tumor, but it is better called Pancoast's syndrome. Most of these cases are examples of apical bronchogenic carcinoma pressing on the brachial plexus and the sympathetic cervical chain, but without symptoms or signs of pulmonary disease. In a few instances the lesion may be an epidermal carcinoma arising from embryonal remains rather than any adjacent normal structure.

**Secondary Tumors.**—Secondary tumors of the lung are very common. Carcinoma may reach the lung by the blood stream or *via* the

lymphatics (cancer of the breast). Many nodules are scattered through one or both lungs, and sometimes these nodules may be miliary in type. Microscopic clumps of tumor cells may be found where no gross tumor can be detected. In some cases the nodules are entirely subpleural, none being found in the substance of the lung. (Fig. 225.) Cancer of the alimentary canal and pancreas naturally metastasize to the liver (portal vein spread) rather than to the lungs. Other forms of secondary tumor are sarcoma, malignant melanoma, chorionepithelioma, and hypernephroma. Sarcoma of bone has a special tendency to metastasize to the lungs. Chorionepithelioma has

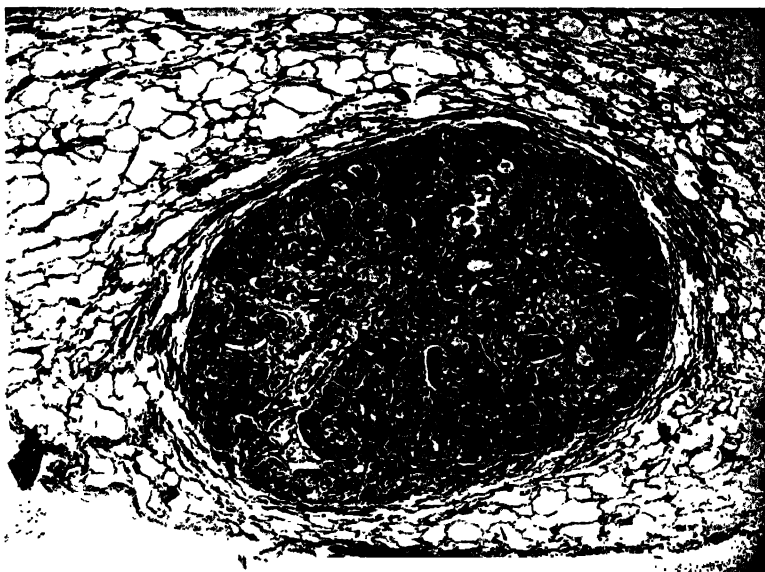


Fig. 225.—Secondary carcinoma of lung lying just under the pleura.  $\times 12$ .

the intensely hemorrhagic character of the primary tumor in the uterus. Hypernephroma forms large masses in the lungs which have a remarkably clear-cut outline in a roentgen-ray picture, the “cannon-ball appearance” of the radiologists.

## THE PLEURA

### PLEURISY

Inflammation of the pleura, pleuritis, or pleurisy must be much commoner than clinical observation would indicate, because adhesions due to a former pleurisy are among the commonest of postmortem findings. Pleurisy may be serofibrinous or purulent, the latter being



usually known as empyema. The common causal organisms are pneumococcus, streptococcus and the tubercle bacillus.

**Serofibrinous Pleurisy.**—The exudate may be mainly fibrin (Fig. 226), the serous effusion being negligible or undetectable clinically. This is known as dry or fibrinous pleurisy. When the exudate is abundant the condition is called pleurisy with effusion. Pleurisy may be secondary to such pulmonary conditions as pneumonia, tuberculosis, carcinoma, and infarct, or to a neighborhood infection such as pericarditis, periostitis of the rib, or peritonitis. In such cases it is likely to be of the dry variety. Or it may appear to be a primary pleural condition, either dry or with effusion. These cases are almost all tuberculous in nature. The infection is not strictly primary, but probably begins in a subpleural focus in the lung from which it spreads to the pleura, both lesions subsequently becoming healed.

**Lesions.** The fibrinous exudate may be so thin as merely to dull the luster of the membrane or so thick that it can be peeled off in layers. Both parietal and visceral layers are involved, and stringy fibrinous adhesions pass between the two layers and also between the lobes. Later these may become converted into permanent fibrous adhesions, and in extreme cases the entire cavity may be obliterated.

The fluid exudate may be very small in amount, as in the dry form, or it may fill the entire cavity. Being an exudate the specific gravity is 1.018 or higher and the protein content 4 per cent or more. The fluid is clear or opalescent, depending on the number of cells it contains. In tuberculous cases these cells are mainly lymphocytes, but in pneumonia polymorphonuclear leucocytes predominate. When the fluid is withdrawn a jelly-like clot forms, owing to the high fibrinogen content. Hemorrhagic effusion indicates malignancy. When the effusion is abundant the lung is collapsed, the heart pushed over to the other side, the diaphragm pushed down, and the intercostal spaces widened.

**Empyema.**—Purulent pleurisy is usually secondary to infection in the lung, sometimes to spread of infection from other organs—such as the pericardium, chest wall, or peritoneum. Pneumococcal empyema



FIG. 226.—Pleurisy showing fibrinous exudate.  $\times 130$ .

complicates lobar pneumonia in a small proportion of cases (2 to 5 per cent). Streptococcal empyemas are often due to rupture of a small subpleural abscess which floods the pleural cavity with the massive dose of organisms needed to produce suppuration. (Fig. 227.) In the streptococcal empyemas which complicate epidemic influenza the exudate apparently begins to form at the commencement of the illness, it accumulates very rapidly, and the chest is full of fluid at the height of the pneumonia. At this time the patient is suffering from acute air hunger, and if the chest is opened to let out the pus,



FIG. 227. —Subpleural abscess about to rupture. Rupture of such an abscess is certain to be followed by empyema.



FIG. 228. —Greatly thickened pleura.  
× 40.

the collapse of the lung and the partial collapse of the other lung (owing to the mobility of the normal mediastinum) may turn the trembling balance against the patient and cost him his life. The danger is the pneumonia rather than the empyema. If the chest is not opened until the pneumonia has subsided it can be done with impunity. Moreover by this time adhesions have converted the mediastinum into a rigid partition so that the opposite lung does not collapse.

The *pleura* is covered by a layer of inflammatory exudate which is much thicker than in the other two forms of pleurisy. This thick

layer covers the parietal as well as the visceral layer, so that an exploring needle may have to be pushed in a long way before it encounters pus. In course of time the exudate becomes converted into fibrous tissue (Fig. 228) and the lung may be bound down to such an extent that it fails to expand when the pus is evacuated. Very dense adhesions are likely to be formed.

The *pus* seldom fills the entire pleural cavity. It is limited to one or two regions by adhesions which pass between the lung and the chest wall (encysted empyema) or between the lobes of the lung (interlobar empyema), so that an empyema is often not a pleural cavity filled with pus, but rather a pocket of pus tucked away in some obscure corner and very difficult to locate with an exploring needle. The nature of the pus varies with the infecting organism. In pneumococcal cases it is thick and creamy, of a yellow or greenish color, while in the influenzal streptococcal cases it is quite watery in the early stages although swarming with streptococci, becoming more frankly purulent later. The pus may rupture through the chest wall or into a bronchus with the establishment of a pleuropulmonary fistula, a condition which may prolong the infection indefinitely.

The *lung* is collapsed to a degree depending on the amount of the fluid. In extreme cases it is flattened against the mediastinum and the posterior chest wall. Pressure of the pus may lead to necrosis and destruction of the lung at the seat of pressure. In long-standing cases there may be a diffuse fibrosis of the lung which combines with the adhesions and the pleural exudate to prevent expansion.

There may be general disturbances such as emaciation, amyloid disease of the liver, spleen, etc., abscess of the brain, and multiple arthritis.

**The Relation of Symptoms to Lesions.**—The symptoms of the various forms of pleurisy are very similar. *Pain* in the side made worse by breathing is the most characteristic symptom. It is not caused by friction of the inflamed and roughened surfaces as is commonly supposed, for the friction rub may still be heard after the pain has ceased, and pleural pain may come on after pneumothorax. Like so many other pains it is due to tension, the inflamed and acutely sensitive parietal pleura being stretched every time the patient takes a deep breath. The visceral pleura is insensitive and so can take no part in producing the pain. Strapping of the chest relieves the pain by preventing the stretching of the parietal pleura; it does not prevent the friction. The pain disappears with the onset of effusion, because the fluid serves as a splint to immobilize the lower ribs. The *friction rub* is heard as long as the roughened surfaces are rubbing against one another; it disappears when the surfaces are separated by effusion. *Cough* is probably due to pleural irritation. *Wasting, loss of strength* and *amyloid degeneration* may occur in empyema due to the great loss of nitrogen from the body in the constant outpouring of pus. The *leucocyte count* depends on the type of lesion. There is more likely to be leucocytosis in the dry than in the moist form of pleurisy. The leucocyte count is high in pneumococcal empyema, but may be normal in the empyema of influenza.

## HYDROTHORAX

Hydrothorax is a fluid transudate, as opposed to an inflammatory exudate, in the pleural cavity. The watery fluid has a specific gravity

below 1.018 and protein content below 4 per cent. It is a part of cardiac or renal edema. For some reason hydrothorax due to cardiac disease is usually right-sided. This may possibly be due to pressure of the dilated right auricular appendix on the pulmonary veins on that side, but it must be admitted that that explanation sounds rather far-fetched. In renal edema the pleural effusion is usually bilateral, and if it happens to be unilateral it is as common on the left as on the right.

**Hemorrhagic Pleural Fluid.**—*Hemothorax* is a condition in which blood is poured into the pleural cavity as the result of rupture of an aortic aneurism, fractured ribs, wounds of the chest, etc. In *hemorrhagic pleurisy* there is hemorrhage into a preëxisting pleural effusion, so that the fluid is watery and bloody but not pure blood. This condition is usually due to carcinoma of the lung, either primary or secondary.

**Chylothorax.**—A milky fluid in the pleural cavity may be chyle, chyliform or pseudochylous. True *chyle* is due to rupture or obstruction of the thoracic duct by trauma, malignant disease, tuberculosis or filaria. *Chyliform* fluids, which closely resemble chylous fluid, are milky due to the presence of fine fat droplets derived from fatty degeneration of cells in cancer of the lung or tuberculosis. A *pseudochylous* fluid does not contain fat, although it may have a milky appearance, which may be due to the presence of albuminous particles in fine subdivision.

### PNEUMOTHORAX

Pneumothorax is air or gas in the pleural cavity, but there is usually an accompanying serous or purulent effusion, so that the condition is really a hydropneumothorax or pyopneumothorax. There is normally a negative pressure in the pleural cavity, and when the cavity communicates with the lung or the outside air rushes in, the negative pressure falls to zero, and as the opening is often valvular a positive pressure may take its place.

Pneumothorax is usually due to rupture of a subpleural tuberculous cavity. Sometimes it is caused by the bursting of an emphysematous bulla. Rarely it may be associated with abscess or bronchiectasis. Laceration of the pleura from without and tearing of the lung by a fractured rib are uncommon causes. Much more rare are perforation of the esophagus and rupture of an ulcer or cancer of the stomach through the diaphragm. There remains a small group of cases of spontaneous pneumothorax, in which the condition suddenly develops without any obvious cause. Some of these may be due to rupture of an emphysematous vesicle.

**Symptoms.**—The onset is often sudden with severe pain in the side and great dyspnea, or it may be quite gradual. The affected side is enlarged and immobile, with lack of vocal fremitus, hyper-resonance, absence of breath sounds, and the characteristically echoing coin sound. When the patient is shaken the Hippocratic succussion splash may be heard in some cases.

**Lesions.**—The air should be demonstrated before the chest is opened at autopsy. A needle may be pushed through the chest wall and the issuing gas may blow out a match. Or the skin may be reflected,

and a small cup made in the intercostal muscles in which water is placed. When the pleura is punctured at this point bubbles of air appear in the water. When the chest is opened fluid will usually be found, which may be serous but is more often purulent (pyopneumothorax). The lung is collapsed, forming a small mass in the region of the hilus. The tuberculous cavity and perforation responsible for the condition can usually be seen. The cavity is usually a small recent subpleural one. The heart is pushed over to the opposite side and the diaphragm pushed down so that its under surface may become convex and the edge of the liver is far below the costal margin.

The lesions of *artificial pneumothorax* produced for the purpose of resting the lung in unilateral tuberculosis are the same as in ordinary pneumothorax. Sometimes an effusion will suddenly appear, probably due to pleural irritation.

**The Relation of Symptoms to Lesions.**—The abrupt onset is due to the air suddenly rushing into a cavity where there is a negative pressure. The pain is caused by stretching of the parietal pleura. The enlargement and immobility of the affected side, hyper-resonance, and coin sound are due to the air which fills the pleural cavity. The dyspnea, lack of vocal fremitus, and absence of breath sounds are caused by collapse of the lung, and the succussion splash is caused by the movement of the fluid. The roentgen-ray picture is highly characteristic (air, fluid, and collapsed lung).

## TUMORS OF THE PLEURA

Tumors of the pleura may be primary or secondary. Primary tumors are rare; secondary tumors (carcinoma) are fairly common.

**Primary Tumors.**—These may be divided into two main groups, the localized and the diffuse. The *localized* tumors are of many histological types, but they have one characteristic in common; they arise from the tissues beneath the surface lining, whereas the diffuse tumors arise from this layer of cells. The localized tumors may grow from the parietal or visceral pleura. The most important member is the so-called giant sarcoma of the visceral pleura, which is of very slow growth and does not infiltrate nor metastasize, so that by the time it is discovered it may attain an enormous size and fill the entire pleural cavity. It has the microscopic structure of a fibrosarcoma, but does not behave like a malignant growth.

The *diffuse* tumor arises from the surface lining cells, and is commonly known as an endothelioma. It would be better called a mesothelioma, as the surface cells are mesothelial in character, the lining of the pleural cavity being derived from the coelomic epithelium, which in turn is developed by a splitting of the mesoderm. The tumor may present characteristics of either epithelial or connective tissue, due to the varied potentialities of the mesothelial cells. It causes a diffuse thickening of the pleura which may extend over a considerable area or even the entire lung and may be over 1 cm. in depth. Both layers of the pleura may be involved. Pleural effusion is common, at first serous and later hemorrhagic. *Microscopically* the tumor consists of large spherical cells arranged in solid masses and columns, often within the lumen of lymphatics; they may have a definite glandular formation as in an adenocarcinoma. The stroma is usually fibrous and abundant.

**Secondary Carcinoma.**—In secondary cancer of the lung the pleura may be involved, but not infrequently the pleura is studded with small tumors although none are to be seen in the lung. Sometimes a network of lymphatics is outlined as a series of white lines due to permeation by carcinoma cells. The primary tumor is usually in the breast.

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## CHAPTER XVIII

### THE MOUTH, NECK, AND ESOPHAGUS

#### THE LIPS

THE important lesions of the lips are cancer, primary syphilis, and angioma.

**Carcinoma.**—Cancer of the lip is one of the commonest forms of malignant disease. But it is only common in one sex (male) and in one lip (lower). It is quite rare in women and in the upper lip. The high incidence in the lower lip may be attributed to its being much more exposed to irritation (biting, pressure of a pipe, etc.). The disease is commonly preceded by some lesion caused by chronic irritation such as fissures, abrasions due to jagged teeth, a patch of seborrhea or leukoplakia, etc.

The disease begins as a local thickening and induration. If growth is mainly toward the surface a warty nodule is formed which soon becomes ulcerated. If growth is deep the chief lesion is a deep-seated induration, and there may be no surface tumor or ulceration for a considerable time. When an ulcer does form it has the usual hard raised edges of a malignant sore.

*Microscopically* the tumor is an epidermoid carcinoma. Masses of squamous cells grow into the deeper tissues, and a varying degree of cell-nest formation and cornification takes place. Most of the cases belong to Grades 1 and 2, and a fair number to Grade 3, but I have never seen a case of Grade 4. It may be pointed out here that a convenient practical method of grouping the tumors of the oral cavity from the point of view of malignancy is as follows: (1) tumors from lips to teeth—mostly low grade; (2) tumors from teeth to back of tongue—increasing in malignancy as we pass back; (3) tumors of pharynx—high grade of malignancy.

**Spread.**—The spread is local, seldom distant. The malignant ulcer may destroy the lip, the skin of the chin, and finally involve the mandible. The submaxillary lymph nodes are involved from the lateral part of the lip, the submental from the central part, but the corresponding salivary glands are seldom involved. The tumor cells may then spread to all the superior cervical lymph nodes, both superficial and deep, but as there is no direct connection between the lip and the inferior cervical and supraclavicular groups, these nodes are seldom involved until very late in the disease. In ulcerating cancer of the lip the lymph nodes under the jaw are often palpable owing to an inflammatory swelling, but they lack the characteristic hardness of malignancy. At the time of diagnosis lymph node involvement is

nearly three times as common in cancer of the tongue and floor of the mouth as in cancer of the lip.

**Syphilis.**—A primary chancre of the lip may be on either lip, but is usually on the upper. It is usually caused by kissing, but an infant may be infected through being suckled by a syphilitic wet-nurse. The lesion begins as a hard nodule which may ulcerate and develop into a typical chancre. There is the usual regional lymph node involvement, the submental and submaxillary nodes becoming enlarged and hard. When ulceration occurs spirochetes are readily demonstrated by the dark-field method.

**Angioma.**—These are not uncommon tumors in children and are probably congenital. Both hemangioma and lymphangioma occur and cause a characteristic diffuse enlargement of the lip. A hemangioma has a bluish color, but a lymphangioma is colorless.

## THE MOUTH

**Stomatitis.**—Inflammation of the mucous membrane of the mouth is commonly due to general rather than local conditions. It may be catarrhal with general redness and swelling of the mucosa, ulcerative with the formation of small superficial ulcers, or gangrenous, a rare form known as *cancrum oris*.

**Tonsillitis.**—Acute tonsillitis may be follicular or parenchymatous. *Follicular* tonsillitis is so called because the inflammation is confined to the lymph follicles surrounding the crypts. The tonsils are large and red, and the surface is covered with yellow spots of pus which can be wiped away. The *parenchymatous* form or *quinsy* is a diffuse inflammation involving the whole tonsil and spreading to the surrounding tissues. Quinsy is characterized by suppuration, swelling of the peritonsillar tissue and deviation of the uvula to one side. The cervical lymph nodes are enlarged and tender, for they also are inflamed. The *microscopic* picture is one of diffuse suppuration.

**Diphtheria.**—The lesions of diphtheria are chiefly in the throat, on the tonsil, pharynx, and soft palate. The lesions are usually localized, taking the form of a gray patch of inflammatory exudate known as a false membrane, which is firmly adherent to the underlying tissue so that when it is removed it leaves a raw surface. *Microscopically* the gray patch is composed of fibrin threads and necrotic epithelium. The fibrin is interwoven with the necrotic cells, thus explaining the firmness with which the exudate is attached. Large numbers of diphtheria bacilli are present in the membrane.

**Vincent's Angina.**—This is a destructive lesion associated with the presence of two organisms, a long fusiform bacillus with pointed ends and a spirochete which stains faintly with ordinary aniline dyes. These Vincent organisms, as they may be called, are probably closely related. They are readily demonstrated in direct smears (not culture),

where the spirochetes may form tangled masses. The lesion, which is usually on or near the tonsil, is at first necrotic, and when the slough has separated a large cavity may be left. Before adopting drastic local treatment of a necrotic gingivitis a leucocyte count should be done to exclude agranulocytic angina.

**Syphilis.**—*Secondary* lesions take the form of bilateral grayish-white patches (mucous patches) like the track of a snail, or superficial ulcers. These lesions may occur on the tonsils, soft palate, or buccal mucous membrane. *Tertiary* lesions are gummata which break down and leave deep, punched-out ulcers. This lesion is most often seen on the hard palate, where it causes perforation of the palate and regurgitation of food through the nose, but it may also occur on the tonsil and fauces.

**Carcinoma.**—Cancer of the mouth is similar to the much commoner cancer of the tongue and will be merely mentioned. It occurs in the lower rather than the upper oral cavity, chiefly on the floor of the mouth, the cheek and the mandible. The lesion is at first a localized thickening, but later becomes a deep excavated ulcer. *Leukoplakia* is a frequent precancerous lesion, often associated with a badly fitting dental plate. Also probably precancerous in character are degenerative mucous membrane changes found in the majority of mouth cancers. These are usually the result of a combination of avitaminosis with various forms of chronic irritation, *e. g.*, tobacco, syphilis, and sepsis (Martin and Koop). Lack of vitamin B is the most frequent deficiency, and probably the most important from the point of view of carcinogenesis. Microscopically oral cancer is an epidermoid carcinoma.

## THE TONGUE

**Inflammation.**—Glossitis or simple inflammation of the tongue may take the form of an acute diffuse inflammation or of ulcers. *Acute glossitis* is not a common condition. It may be caused by the sting of a bee, an infected wound, etc. There is rapid swelling of the tongue and suppuration, and the patient may be nearly choked before the pus is let out. *Simple ulcers* occur at the edge or tip of the tongue, and are often due to the irritation of a jagged tooth or badly-fitting plate. The ulcer is at first shallow and acute in type, but if the irritant is not removed it may become more chronic with indurated edges, and may eventually become malignant. Shallow painful ulcers, usually of short duration, often develop in the mouth and on the tongue as the result of constitutional disturbances. Some persons are particularly susceptible. The pathogenesis of these lesions is not clear; they are probably surface infections. The condition commonly called *chronic glossitis* is nearly always syphilitic, and will be described under that heading.

**Syphilis.**—A syphilitic lesion of the tongue may be primary, secondary or tertiary. A *primary chancre* presents the usual appearance of the hard sore. Spirochetes can be demonstrated by the dark-field.

The induration of the lesion and the fact that lymph nodes in the floor of the mouth are enlarged and hard may easily lead to a mistaken diagnosis of carcinoma, a much commoner condition. The *secondary* lesions are mucous patches or shallow ulcers. They are swarming with spirochetes and are highly infectious. The *tertiary* lesions may take the form of an ulcer or a diffuse glossitis. A *syphilitic ulcer* is caused by the breaking down of a gumma and is usually situated on the dorsum of the tongue. It is liable to be mistaken for carcinoma, but it seldom shows the same degree of induration and the regional lymph nodes are not enlarged.

*Syphilitic glossitis* may be superficial or deep. In the *superficial* form there is usually some surface irritant at work, such as smoking a hot pipe or drinking strong spirits. Syphilitic inflammation of the deeper layers of the mucosa is followed by a heaping up of the surface epithelium, with the formation of lozenge-shaped white patches often separated by painful cracks and fissures which give a mosaic-like appearance to the dorsum of the tongue known as *leukoplakia*. This surface proliferation is caused largely by the accessory irritant referred to above. Syphilitic leukoplakia is an important predisposing factor to malignant disease (precancerous lesion), the cancer being especially apt to develop in one of the deep cracks. Epithelial proliferation with leukoplakia does not always occur, and the surface of the tongue may be smooth, red, and atrophied due to obliteration of the papillæ by the inflammatory process. The *deep* form of syphilitic glossitis also acts as a predisposing cause to carcinoma. The usual syphilitic inflammatory tissue is formed in the depths of the tongue, and the subsequent fibrosis causes scarring, fissuring, and the formation of irregular nodules on the surface giving an appearance which is highly characteristic. One of the commonest manifestations of syphilitic glossitis is marked hypertrophy and enlargement of the tongue, a *luetetic macroglossia*, sometimes so extreme in degree that the tongue may fill the entire mouth. In any case of macroglossia it is well first to think of the possibility of syphilis.

**Carcinoma.**—Cancer of the tongue shows the same strong sex incidence as cancer of the lip, being quite rare in women. It seldom develops in a healthy tongue, being preceded by such precancerous conditions as chronic ulceration and syphilitic glossitis (leukoplakia, cracks, etc.). When a patient with a chronic ulcer on the dorsum of the tongue is found to have a positive Wassermann reaction, the case should be regarded as malignant until proved otherwise by biopsy. The tongue is divided into two portions by the V-shaped line of circumvallate papillæ, the anterior two-thirds and the posterior one-third. Cancer of the anterior two-thirds is epidermoid in type, usually of distinctly higher grade than cancer of the lip. The edge is the common site, but the tumors which develop on a syphilitic basis are often on the dorsum. Cancer of the posterior third is fortunately much rarer, for it is usually markedly malignant although at the same time markedly radio-sensitive. It is likely to be a high-grade epidermoid or occasion-

ally a transitional-cell carcinoma. The *gross appearance* at first presents merely a local induration; this may develop into a warty mass with early ulceration, but often the tumor takes a form of a deep infiltration and ulceration may be late. The malignant ulcer is characteristically hard with raised, indurated, rounded edges. Extensive necrosis, sloughing, destruction, and secondary infection constitute the finish of the picture. The *microscopic appearance* has already been indicated, *i. e.*, epidermoid or transitional-cell (posterior third). *Spread* is rapid, so that it is of the first importance not to temporize with a suspicious ulcer or indurated patch on the tongue. Time should be measured here in days, whereas in a similar lesion of the lip it may be measured in weeks or even months. An immediate biopsy is imperative. The most important reasons for the rapid spread are: (1) the extremely rich lymphatic drainage of the tongue, (2) the constant muscular movements, and (3) the high grade of the tumor. Lymph spread takes place into the submental and submaxillary lymph nodes, into the superior and inferior deep cervical nodes, and even into the supraclavicular nodes. In tumors of the posterior third the upper deep cervical group on both sides of the neck may be involved. Blood spread to distant organs is comparatively rare.

**Tuberculosis.** — For practical purposes tuberculosis of the tongue may be taken to be secondary to pulmonary tuberculosis. It is remarkable how uncommon a complication it is.

The squamous epithelium evidently acts as an efficient protection against the countless tubercle bacilli which must pass over it in a case of active phthisis. The lesion usually commences as an ulcer near the tip of the tongue with sinuous undermined edges, pale watery-looking granulations, and an absence of the induration characteristic of malignant disease. Nevertheless the condition is frequently mistaken for carcinoma. Sometimes it begins as a nodule which ulcerates later. (Fig. 229.)



FIG. 229.—Tuberculosis of tongue not yet ulcerated.  $\times 90$ .

**Ulcers of the Tongue.**—It is evident that an ulcer of the tongue may be inflammatory (simple), malignant, syphilitic, or tuberculous. A *simple* ulcer occurs on the edge or tip, is shallow and inflamed, and is often associated with a sharp tooth or jagged plate. A *malignant* ulcer occurs on the edge or center, is peculiarly hard with raised edges, and may be associated with syphilitic glossitis and enlargement of the regional lymph nodes. A *syphilitic* ulcer occurs on the dorsum, is serpiginous in outline, and is usually a tertiary lesion. A *tuberculous* ulcer occurs at the tip, has undermined edges without induration, and is secondary to pulmonary tuberculosis.

**Innocent Tumors.**—*Angioma* forms a soft bluish mass in the tongue, and is usually congenital. *Lymphangioma* causes a diffuse congenital enlargement (macroglossia). *Dermoid cysts* may occur under the tongue. A *thyroglossal cyst* at the upper end of the thyroglossal duct may form a swelling at the base of the tongue.

## THE PHARYNX

Many of the lesions of the pharynx have already been discussed in connection with the mouth, but one or two remain to be considered.

**Retropharyngeal Abscess.**—Pus may be formed as the result of suppuration in the loose tissue between the posterior wall of the pharynx and the vertebral column. It usually occurs in children suffering from some debilitating illness, and comes on acutely with rigidity of the neck, pain on swallowing, loss of voice, and a tense bulging on the posterior wall of the pharynx indicating the presence of pus. In tuberculosis of the cervical spine a chronic (cold) abscess may form in the same situation. *Ludwig's angina* is an acute diffuse streptococcal cellulitis involving the neck and tongue as well as the structures at the back of the throat. It usually occurs as a complication of one of the streptococcal fevers such as scarlet fever or erysipelas. There is a brawny induration of the neck with pressure on the trachea and edema of the glottis. The condition usually proves fatal in the course of a few days.

**Tumors of the Pharynx.**—A malignant tumor of the pharynx is likely to be an epidermoid carcinoma, transitional-cell carcinoma, lympho-epithelioma or lymphosarcoma.

**Epidermoid Carcinoma.**—This may commence in the pharyngeal wall, the tonsil, or the soft palate. It produces a characteristic induration and soon ulcerates, leading to great destruction of the deeper tissues with secondary infection and a very foul breath. The lymph nodes at the angle of the jaw become enlarged and hard. Willis has pointed out that invasion of the jugular vein is a fairly common occurrence in epidermoid carcinoma of the head and neck with visceral metastases, especially in the liver. *Cancer of the hypopharynx* (postericoid carcinoma) is confined almost exclusively to women. This is the only malignant tumor of the alimentary canal which has this sex incidence.

It is often preceded over a number of years by a combination of dysphagia, dry atrophy of the pharyngeal mucosa, and hypochromic anemia (Plummer-Vinson syndrome). Both the anemia and the mucosal change have a dietetic iron-deficiency basis. The mucosal atrophy seems to act as a precancerous lesion. Adequate treatment of the anemia with iron may therefore prevent the onset of the cancer.

*Transitional-cell Carcinoma and Lympho-epithelioma.*—There is difference of opinion as to whether these tumors are separate entities or are variants of the same lesion. The gross character and the method of spread is similar, so that they may be considered together. The tumor arises from epithelium covering lymphoid tissue, and originates in the nasopharynx, oropharynx and laryngopharynx (sinus pyramiformis). Its chief characteristic is that the primary tumor, while still small and undetected, may give rise to large secondary growths in the cervical lymph nodes on both sides. The growth is centrifugal rather than centripetal. There is often invasion of the base of the skull with involvement of the cranial nerves, particularly the fifth and sixth. The growth may penetrate the cranial cavity. Secondary growths may occur in the lungs and liver at a later date. The tumor is markedly radio-sensitive, and the mass in the neck may melt away for a time. *Microscopically* the transitional-cell carcinoma is highly anaplastic, consisting of sheets of large pale cells showing numerous mitotic figures with no attempt at cornification. The lympho-epithelioma presents a similar picture, but in addition groups of lymphocytes are mingled with the epithelial cells, or they may be scattered more diffusely among these cells.

*Lymphosarcoma.*—This may arise in the tonsil or in the lymphoid tissue of the naso-pharynx. The tonsillar cases are at first unilateral. The cervical and axillary lymph nodes are involved, and later the lymphoid tissue in the rest of the body. *Microscopically* the tumor may be of the lymphocytic or the reticulo-endothelial type.

## THE NECK

The severe *inflammations* of the neck (Ludwig's angina and retropharyngeal abscess) have already been considered. Boils and carbuncles are common on the back of the neck owing to the friction of the collar.

**Cysts.**—A cyst of the neck may be mesial or lateral. The former is a thyroglossal cyst, the latter may be a branchial cyst or a cystic lymphangioma.

**Thyroglossal Cyst.**—The thyroglossal duct is a vestigial structure which passes from the foramen cecum at the base of the tongue to the isthmus of the thyroid gland. If a portion of the duct remains unclosed a cyst is formed lined by columnar epithelium. Such a cyst must always be in the middle line. It is usually below the hyoid bone, but occasionally is at the base of the tongue.

**Branchial Cyst.**—This is formed from an unclosed portion of a branchial cleft, usually the third, and is therefore at the level of the hyoid bone. If it arises from the second cleft it lies just below the mastoid process and projects into the mouth. The cyst is usually lined by columnar ciliated epithelium, but when quite superficial it is lined by stratified epithelium. The wall contains much lymphoid tissue. If the outer end of the cleft remains open the condition is a *branchial fistula*, which opens on the neck at the level of the angle of the jaw.

**Cystic Lymphangioma.**—The vessels of a lymphangioma may undergo marked dilatation so as to form a soft cystic swelling, usually in the anterior triangle of the neck, but sometimes in the axilla or on the chest wall. It is a congenital condition and is usually seen in children, tending to undergo spontaneous cure before adult life is reached. It is

subject to recurring attacks of inflammation which probably play a part in the cure by closing the vessels. It is known clinically as *cystic hygroma* (fluid tumor), and may attain a very large size.

**Tumors.**—Tumors of the neck may be primary or secondary. Primary tumors may be accessory thyroid tissue (considered in connection with the thyroid gland), lymphoblastoma, branchial cleft carcinoma, and carotid body tumor. Secondary tumors are examples of carcinoma. Salivary gland tumors are considered separately (see below).

**Lymphoblastoma.**—Enlargement of the cervical lymph nodes may be due to any member of the lymphoblastoma group, *i. e.*, lymphosarcoma, Hodgkin's disease, and lymphatic leukemia. The disease often commences in the cervical group involving first one and then both sides. Later the lymph

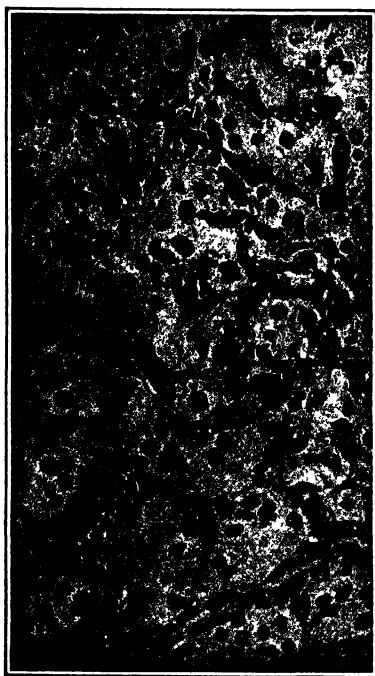


FIG. 230.—Carotid body tumor.  $\times 275$ .

nodes throughout the body become enlarged. In leukemia the blood shows the characteristic leukemic change.

**Branchial Cleft Carcinoma.**—This rare tumor arises from remnants of branchial cleft epithelium. It is very much commoner in males than females. The tumor forms a very hard mass which starts deep in the neck near the bifurcation of the common carotid artery and infiltrates the surrounding tissue. The growth is a squamous-cell carcinoma, but with little tendency to cornification or cell-nest formation.



**Carotid Body Tumor.**—This is a firm, round, slowly-growing tumor in the bifurcation of the common carotid artery. The tumor may grow around the artery, so that the vessel becomes embedded in the tumor, making removal a matter of great difficulty. The carotid body belongs to the chromaffin system, and the tumor may be regarded as a chromaffinoma of benign character. The cells, which are arranged in groups or sheets, are large, granular, and polyhedral, and may contain chromaffin substance. (Fig. 230.)

**Secondary Carcinoma.**—Epidermoid carcinoma of the lip, tongue, mouth, larynx, and esophagus may metastasize to the cervical lymph nodes. The transitional-cell type of carcinoma with a small often undiscovered primary growth in the pharynx or nasopharynx and large secondary tumors in the neck has already been described. Finally there may be lymphatic spread of carcinoma from more distant organs. Owing to the fact that the thoracic duct receives efferents from the supraclavicular and lower deep cervical nodes on the left side before it opens into the innominate vein, these nodes are often involved in abdominal and thoracic cancer. Gastric and bronchogenic carcinoma are the most frequent primary tumors responsible, but even the most distant tumors (ovarian, uterine, testicular) may metastasize to the neck by this route. Malignant supraclavicular nodes on the right side suggest cancer of the right lung (right lymphatic duct).

## THE SALIVARY GLANDS

The parotid gland is more liable to disease than the submaxillary and sublingual, so it will be taken as the type.

**Acute Inflammation.**—This may be suppurative or non-suppurative. In *suppuration* the infection may be hematogenous as in acute fevers and pyemia. This is rare. Infection from the mouth by way of Stenson's duct is more common. The pus is prevented from reaching the surface by the dense fascia which covers the gland. It may form a retropharyngeal abscess.

The *non-suppurative* form is *mumps*, one of the commonest diseases of childhood. The gland on both sides is acutely inflamed, swollen, painful, and tender. There is little to be seen in the gland apart from a serous exudate. As there is no suppuration or necrosis, healing is by resolution and the gland is uninjured. A similar lesion is produced in monkeys by a filterable virus from the saliva in cases of mumps. Orchitis (inflammation of the testicle) is a common complication in the adult, but here recovery may not be complete and the testicle may undergo atrophy.

**Mixed Tumors.**—This is the condition commonly called parotid gland tumor but, as it may occasionally occur in any of the salivary glands, in the mucous membrane of the mouth, and in the palate, this name is undesirable and misleading. It is a fairly common slowly-growing tumor of early adult and middle life which begins either in the substance or the surface of the salivary gland, and may continue to increase in size for many years, but at any time growth may stop.

It is inherently benign, but after the usual operative procedure (enucleation of the tumor) there is recurrence in from 20 to 45 per cent of cases, the tumor then becoming locally destructive and invasive. Total excision of the gland with removal of the capsule gives infinitely better results. Sometimes after growing slowly for many years it may take on rapid growth and invade the surrounding tissue. The lymph nodes are rarely involved unless the tumor has been interfered with. It is usually encapsulated, but may not be.

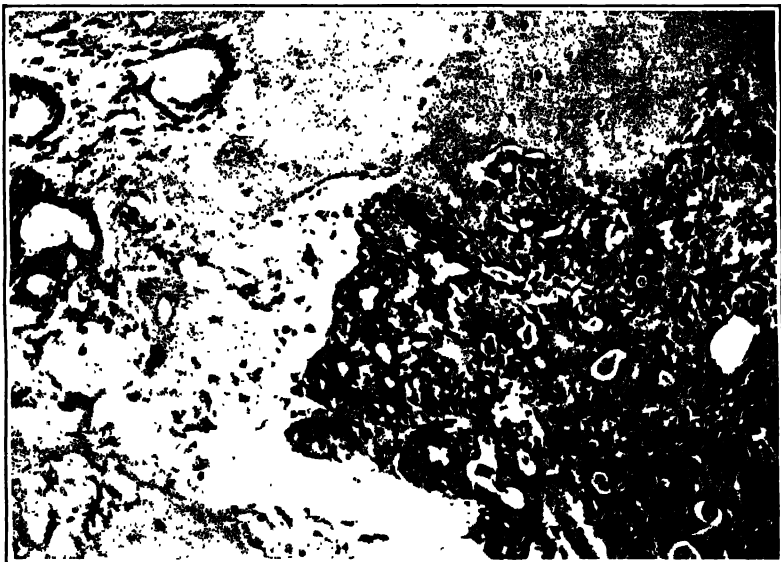


FIG. 231.—Mixed tumor of the parotid. Cartilage above, glandular tissue to the right, mucoid tissue to the left.  $\times 160$ .

The *microscopic appearance* is varied and perplexing, for the tumor appears to consist of both ectodermal and mesodermal elements. It is for this reason that it is called a mixed tumor. The following elements are commonly present in one or other part of the tumor, although it is very difficult to find them all combined in a single microscopic field (Fig. 231): (1) masses of epithelial cells often showing a glandular arrangement, (2) mucoid connective tissue with evidence of production of mucin, (3) cartilage, and (4) lymphoid tissue. The cartilage has been the chief stumbling block, as it seemed to be mesodermal in origin, while the epithelium was of ectodermal origin.

The *nature of the tumor* has long been a subject for discussion. It is possible that some of the tumors may arise as the result of the accidental sequestration of embryonal cells during the early and complicated development of the face; such tumors would be true "mixed tumors." It appears probable, however, that the great majority are not really mixed tumors, but are benign epithelial growths (adenomas)

of the salivary glands. The difficulty presented by the cartilage is removed by the discovery that this material is not true cartilage. The tumor epithelial cells produce mucin, and this constitutes the origin of the mucinous "connective tissue." This myxomatous material, which stains well with mucicarmine, is homogenous like cartilage, and the cells which it contains may lie free in small spaces around which there may be a fibrillar condensation, so that a pseudocartilage may be produced. It is also possible that true cartilage may be formed from this material. Simard has reported a sweat gland adenoma of the palm with a structure identical with that of mixed tumor of the parotid. In this case the mucous secretion of the epithelial cells had undergone metaplasia into cartilage.

Hellwig points out the resemblance of mixed tumors to the developing notochord, and suggests that these tumors are derived from misplaced elements of that structure. The notochord is in contact with the buccopharyngeal membrane, and on the rupture of that membrane the cells of the two structures may be intermingled. It may be noted that the notochord comes into intimate relation with the developing parotid gland, the submaxillary gland, and the palate, the three common sites of mixed tumors.

**Carcinoma.**—Carcinoma of the salivary glands grows rapidly, infiltrates the whole gland, involves the regional lymph nodes and sets up distant metastases. The tumor may be adenocarcinomatous, medullary, or anaplastic in type. The last-named is usually mistaken for round-cell sarcoma.

**Adenolymphoma.**—This rare tumor of the salivary glands usually occurs in the parotid in the fifth and sixth decades. It is benign, slowly growing, well encapsulated, and much commoner in males than females. The microscopic picture is characteristic: tubular alveoli lined by tall columnar epithelium supported by an abundant lymphoid stroma with active germ centers. (Fig. 232.) There may be cystic spaces with papillary projections. This tumor is also called an *onkocytoma*, because it has been suggested that it may arise from a special type of cell found in the parotid with advancing years characterized by its size (*onkos*, bulk), and known as an onkocyte.

**Mikulicz's Disease.**—Mikulicz's disease is a very rare condition in which there is enlargement of the lachrymal and salivary glands on both sides. It is sometimes associated with leukemia, and in the later stages the lymph nodes, spleen and liver may be enlarged. It would perhaps be well to divide the condition into Mikulicz's disease proper and the Mikulicz syndrome. In *Mikulicz's disease* proper the enlargement is confined to the lachrymal and



FIG. 232.—Adenolymphoma of parotid gland.  $\times 100$ .

salivary glands without involvement of the lymphatic system and without change in the blood. In the *Mikulicz syndrome* the glandular enlargement is part of a lymphoblastomatous condition such as leukemia, lymphosarcoma or Hodgkin's disease. *Microscopically* the gland structure is replaced by small round cells or larger cells of the Hodgkin type. The condition may be regarded as a localized form of lymphoblastoma related to leukemia and Hodgkin's disease.

**Uveo-parotid Fever.**—This is a clinical syndrome characterized by chronic inflammation of the uveal tract (iris, ciliary body, choroid) and both parotids. The parotids are swollen, and the occasional enlargement of both lachrymal glands may lead to a mistaken diagnosis of Mikulicz's disease. Irido-cyclitis and facial paralysis are common. The course is generally febrile, but there is a marked tendency to spontaneous recovery. The condition used to be regarded as a low grade form of tuberculosis, but it is now believed to be a variety of sarcoidosis.

**Salivary Calculi and Cysts.**—A *salivary calculus* usually forms in Stenson's ducts, and the saliva collects above the obstruction during a meal, causing a cystic swelling of the parotid which gradually subsides after the meal. A *ranula* is a cyst of the sublingual gland, and is therefore situated in the floor of the mouth under the tongue, where it forms a bluish nodule. Occasionally the submaxillary gland is involved.

## THE ESOPHAGUS

The common lesions of the esophagus are carcinoma, stricture, and diverticulum.

**Carcinoma.**—Cancer of the esophagus shows the usual sex incidence of alimentary canal neoplasms, over 80 per cent being in men. Cancer of the hypopharynx (postcricoid cancer) is sometimes included with cancer of the upper end of the esophagus; indeed it is often impossible to determine in which region the tumor originated. When this is done the sex incidence of upper end tumors is overwhelmingly female. The commonest site is the middle where the esophagus is crossed and constricted by the left bronchus, followed rather closely by the lower end. The middle, which is the narrowest part, and the lower end are the regions where irritants (food and drink) are delayed longest. The least common site is the upper end, but if cancer of the hypopharynx is included, the incidence practically equals that of the lower end. The tumor begins as a nodule in the mucous membrane, and sometimes grows into the lumen as a bulky mass, but usually takes the form of a diffuse infiltration which slowly encircles the esophagus and causes marked narrowing of the lumen with dilatation of the proximal part of the tube. Ulceration of the surface occurs sooner or later, and the growth may ulcerate into the trachea, into the aorta with fatal hemorrhage, or into the mediastinal tissues with gangrenous inflammation. The stenosis gives rise to marked difficulty in swallowing. The prognosis used to be hopeless, but modern surgery can remove the diseased esophagus and provide the patient with a new one. The earliest diagnosis can be made with the aid of the esophagoscope. *Microscopically* the tumor is an epidermoid carcinoma, but usually

without epithelial pearls or much cornification. Occasionally it may be an adenocarcinoma, which probably arises from anomalous glands in the wall of the esophagus identical with the gastric glands.

*Spread.*—Spread, as is usual in epidermoid carcinoma, is to the regional lymph nodes. These may be mediastinal, cervical, or abdominal. If the cancer is at the upper end of the esophagus, the cervical as well as the mediastinal glands will be involved; a tumor in the middle of the esophagus will spread to the mediastinal glands; with tumors of the lower end, metastases are formed below the diaphragm in the coelic chain of glands and in the liver.

**Stricture.**—Stricture of the esophagus may be organic or functional.

*Organic or cicatricial stricture* is caused by scar formation due to the swallowing of corrosive or boiling fluids, and more rarely to laceration produced by impacted foreign bodies. Fibrous tissue is produced as the result of the injury usually at the upper or lower ends, and this becomes dense scar tissue which encircles the esophagus and causes an extreme degree of stenosis which it may be very difficult to dilate. The esophagus may be narrowed owing to pressure from without by an aneurism of the aorta, a tumor of the lung, or a mass of enlarged lymph nodes.

*Functional or spasmodic stricture or cardiospasm* occurs in young men and women of neurotic temperament. The muscular sphincter at the lower end of the esophagus and the cardiac end of the stomach remains closed and thus prevents food from entering the stomach. The esophagus immediately above the site of the spasm may become dilated and hypertrophied. The distention may become much more extreme than in organic stricture, because there is more time for it to develop, as the patient may live for many years. In middle-aged women and more rarely in men there may be *dysphagia with anemia*. (Plummer-Vinson syndrome.) Here the cricopharyngeus sphincter between pharynx and esophagus remains closed and fails to open during deglutition. The anemia is probably secondary to the deficient dietary. The mucous membrane of the pharynx and tongue is dry and parchent-like. In the roentgen-ray picture the lower end of the esophagus presents a characteristic blunt-pointed appearance, like the end of a cigar, quite different from the appearance in carcinoma. It is probable that both of these forms have a neurogenic basis, a preponderance of sympathetic activity over that of the vagus. In some cases of cardiospasm, inflammatory lesions of Auerbach's plexus have been found at the lower end of the esophagus. It is possible that the condition is rather an inability of the sphincter to relax than an actual spasm, to which the name *achalasia* (*a*, not + *chalis*, relaxation) is applied. This may also be the basis of Hirschsprung's disease, where a persistently closed rectal sphincter leads to great dilatation of the colon in children.

**Diverticula.**—A diverticulum of the esophagus may be of the anterior or posterior variety. The *posterior* variety is much the commoner. It is really a pharyngeal rather than an esophageal diverticulum,

occurring in the pharyngeal wall at its junction with the esophagus. It is usually found in men of middle age. The chief cause is probably prolonged intrapharyngeal pressure due to failure of what Chevalier Jackson calls the "cricopharyngeal pinchcock" to relax during swallowing. The mucous membrane of the lower part of the posterior wall of the pharynx becomes protruded between the oblique and transverse fibers of the cricopharyngeus muscle, so that a sac is formed behind the esophagus which pushes that structure forward. The condition tends to become steadily worse through the accumulation of food in the sac, and pressure on the esophagus may cause difficulty in swallowing. The *anterior* variety occurs at the level of the bifurcation of the trachea, and is due to traction of tuberculous tracheo-bronchial lymph nodes which have become adherent to the esophagus. The posterior form is thus a pulsion diverticulum, the anterior form a traction diverticulum.

*Varices* may occur at the lower end of the esophagus in cirrhosis of the liver. Rupture of these varicose veins may cause fatal hemorrhage. *Rupture of the esophagus* may be *traumatic* (due to passage of a bougie or esophagoscope), or spontaneous. *Spontaneous* rupture is a rare condition which occurs after prolonged vomiting and is probably due to acute inflammation of the lower end of the esophagus. The pleural cavity is filled with dirty fluid, and the condition is rapidly fatal. *Digestion* of the esophagus may be *postmortem* or *antemortem*. The former is associated with postmortem digestion of the stomach. *Antemortem digestion* is not uncommon and can be distinguished from postmortem digestion by the presence of an inflammatory reaction in the wall of the esophagus. It occurs in postoperative conditions with marked vomiting, and is probably due to retention of acid vomited material in the lower part of the esophagus. Perhaps a better name is acute ulcerative esophagitis. The lesions are ulcerations and the ulcers vary in type from mere superficial erosions to deep perforating lesions. Only the lower part is involved. It may lead to rupture, and at autopsy the pleural cavity is filled with stomach contents. *Leukoplakia* is not uncommon in the lower part of the esophagus. *Tuberculous* and *syphilitic ulcers* are rare conditions. *Fibromas* and other innocent tumors sometimes occur and form polypi. *Sarcoma* is very rare.

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## CHAPTER XIX

### THE STOMACH AND DUODENUM

#### GASTRITIS

INFLAMMATION of the stomach, either acute or chronic, is due to the action of irritants. But the irritant does not necessarily act on the surface. The most important part of the gastric mucous membrane is not the surface epithelium but the deep portion containing the gastric glands, and this deep portion is more likely to be reached by an irritant carried by the blood stream than by mere surface irritation. The causes of gastritis are not very certain, but they may be divided into: (1) surface irritants such as alcohol, irritating foods, and corrosive poisons, and (2) blood-borne irritants, *e. g.*, bacteria.

**Acute Gastritis.**—Surface irritants may readily cause an acute gastritis, which must be present to some extent after every severe alcoholic bout, and is largely responsible for the “morning after” feeling. It may also occur in the acute fevers. The mucosa is reddened and shows as a rule merely catarrhal changes. It is difficult or impossible to separate these from the postmortem changes which invariably occur as the result of digestion unless formalin be injected into the abdominal cavity immediately after death, in which case the gastric mucosa is as fresh and well fixed as if it had been removed at operation. The action of *poisons* on the stomach has already been considered in Chapter XIII. It may be repeated here that carbolic acid coagulates and fixes the mucosa perfectly, the corrosive acids produce destruction and often perforation, and the caustic alkalis cause necrosis with marked softening so that here also perforation may occur. *Membranous gastritis* and *phlegmonous gastritis* are rare conditions in which there is extensive invasion of the stomach wall by bacteria, often streptococci, with violent inflammation and necrosis over a wide area and to a great depth.

**Chronic Gastritis.**—The causes of chronic gastritis are not well understood. Alcohol is always incriminated, but in gastroscopic examinations made by Gray and Schindler on 100 alcoholic addicts who had consumed an average of 2.8 pints of alcohol daily for more than twenty years, the stomach was essentially normal in 55 per cent, nor was any correlation observed between the incidence or severity of the gastritis and the duration of the alcoholism or the amount of alcohol consumed. Almost identical findings are reported by Berry. The disease takes two forms, hypertrophic and atrophic. *Hypertrophic gastritis* is the commoner of the two. There is marked thickening of the mucosa, especially in the pyloric region. The surface becomes



divided into little areas so as to have a finely nodular appearance, a condition known as *état mammelonné*. The polypoid formation known as *gastritis polyposa* is neoplastic rather than inflammatory and will be considered in connection with tumors. *Microscopically* the glands of the mucosa are separated by a diffuse infiltration of lymphocytes, plasma cells, and eosinophils, with a varying degree of fibrosis in the submucous coat. The glands suffer and atrophy, some become cystic, but most of them disappear, so that the mucosa is a mass of granulation tissue covered by epithelium rather than a parenchymatous structure. Such a mucous membrane cannot be expected to secrete hydrochloric acid, so that achylia gastrica develops.

*Atrophic gastritis* may probably be a sequel to the hypertrophic form or may develop independently. It is often associated with constitutional disturbances, especially pernicious anemia. The mucosa is markedly thinned, the glands atrophic and widely separated, the muscle fibers attenuated, and all the coats more or less fibrosed. As the secreting membrane is so atrophic, achylia gastrica is always marked.

**Effects of Gastritis.**—Chronic gastritis in the pyloric region may give rise to the classical symptoms of gastric ulcer, *i. e.*, hunger pains, hypersecretion, and delayed emptying and stasis, but when gastrectomy is done no ulcer is found. European investigators find that gastric ulcer and chronic gastritis are frequently associated, and believe that the gastritis precedes the ulcer. In surgical material it is certainly the case that some degree of gastritis is almost always present in gastric and duodenal ulcer. When the gastritis is at all diffuse there is likely to be *achylia gastrica*. This is a very common consequence of chronic alcoholism, especially in elderly persons. Achylia may be due to hematogenous infection in the infective fevers such as influenza and typhoid, and may persist for years afterward. It occurs in over 30 per cent of cases of pulmonary tuberculosis, and in many cases of the toxemia of pregnancy. Complete achylia is always present in pernicious anemia and usually in cancer of the stomach.

## PEPTIC ULCER

The stomach and the first part of the duodenum are both derived from the foregut, are both supplied with blood from the celiac axis, and are both bathed by acid gastric juice, as the alkaline bile and pancreatic secretion flow into the second part of the duodenum. Ulcer of the duodenum is for practical purposes ulcer of the first part, and as gastric and duodenal ulcers are essentially the same in their pathology and are dependent for their production on the peptic juice, they may be considered together under the heading of peptic ulcer. Peptic ulcers also occur on the jejunal side of a gastro-enterostomy and in Meckel's diverticulum.

**Etiology.**—The cause of peptic ulcer has long been a matter of debate, nor has any agreement yet been reached. The ulcer is pro-

duced by the action of the gastric juice, but no one has explained how it is that the stomach does not digest itself. Living healthy tissue evidently resists digestion, for when kidney or spleen with circulation intact are introduced into the stomach they are not digested, even when the cut surface is exposed to the gastric juice for weeks or months. A peptic ulcer, and in particular a chronic ulcer, is the result of the continued action of the gastric juice on an area of mucous membrane which is presumably of lowered resistance. The real difficulty is to decide the cause of the lowered resistance. There are three principal views: the infective, the chemical and the neurogenic.

A plausible and popular theory is that *hematogenous infection* with organisms of low grade virulence may cause inflammatory foci in the stomach wall leading to necrosis with subsequent digestion and ulcer formation. These organisms are supposed to be non-hemolytic streptococci from foci of infection in the nose, throat and apical tooth abscesses. Small inflammatory foci are often found in the base of the ulcer, but these may be the result of the ulceration rather than its cause.

In a large series of cases Hebbel found that an atrophic gastritis (gastritis leading to atrophy) affecting the antrum was an invariable accompaniment of gastric and duodenal ulcer. It seems reasonable to suppose that the gastritis precedes and is the anatomical basis for the development of ulcer, and that chronic ulcer does not develop in a healthy mucosa. Gastritis is not nearly so frequent an accompaniment of gastric carcinoma, nor is it confined to the antrum.

Cushing has revived the *neurogenic theory* that abnormal vagal impulses from the hypothalamic region of the diencephalon are responsible for vascular spasm and ischemia which cause the initial area of necrosis. Ulcer may complicate tumors of this region, and cerebral injury in the new-born may be associated with erosion and melena. It is undoubtedly more common in the nervous high strung patient, in whom worry and strain may precipitate an attack. The neurogenic factor is the most important single etiologic agent in many cases of ulcer. The paramount importance of this factor is emphasized by the spectacular therapeutic results which follow bilateral division of the vagus nerves (vagotomy), the gastric secretion being greatly reduced and the ulcers tending to heal.

According to the *chemical theory* the essential factor is the action of excess acid. Hyperacidity is a constant accompaniment of peptic ulcer in the early stages, although it may disappear in old chronic ulcers. The fact that the ulcer occurs in non-acid-producing mucosa although in immediate juxtaposition to acid-producing mucosa must be significant. Of even greater significance is the fact that peptic ulcer occurs in a Meckel's diverticulum containing acid-producing gastric mucosa. My colleague, Dr. W. L. Robinson, has a case of peptic ulcer in a teratoma; here, surely, all factors other than chemical may be excluded. Worry and nervous strain are associated with hyperacidity, perhaps explaining the prevalence of ulcer amongst surgeons. It has already been pointed out that the ulcer patient is frequently

nervous and high strung. Food which causes hypersecretion may lead to the formation of ulcer. Thus in Abyssinia, where peptic ulcer is extraordinarily common, a favorite and universal sauce contains 50 per cent cayenne pepper (Bergsma). The experimental injection of histamine, which stimulates gastric acidity, results in the production of ulcers, especially when the histamine is implanted in beeswax to prolong its action. In severe burns histaminoid substances are produced, and it has long been known that such burns may be accompanied by the formation of acute ulcers in the stomach and particularly in the first part of the duodenum, a condition long known as *Curling's ulcer*. This type of ulcer is found in 12 per cent of dogs in which large burns were produced, and Hartman points out that these ulcers are ten times commoner when petrolatum and other similar dressings were used than when the tannic acid method was employed. This difference he attributes to such factors as loss of plasma, infection and acidosis which are prevented by tannic acid dressings. The subcutaneous injection of posterior pituitary extract produces acute hemorrhagic lesions, whilst repeated injections produce chronic ulcers of the peptic ulcer type (Dodds). If the stomach contents are rendered alkaline, injection of pituitary extract fails to produce ulcers. The most effective method of inducing an ulcer to heal, provided it is not too chronic, is by neutralizing the gastric acidity, especially by means of the continuous drip method. All of these facts point to the paramount importance of gastric acidity in the production and maintenance of peptic ulcer, although they do not prove that some additional factor may not also be operative.

That food deficiency may play a part in some regions is suggested by the extreme frequency of duodenal ulcer in Southern India, particularly Travancore (Somervell). In this district food consists of rice and curry, poor in all the vitamins, particularly A and B<sub>2</sub>. In some parts of India, such as the Punjab, where the diet is rich and well-balanced, peptic ulcer is singularly rare.

**Symptoms.**—The chief symptom of peptic ulcer is pain which is relieved by the taking of food. In duodenal ulcer the sequence is food—comfort—pain, whereas in gastric ulcer it is usually food—comfort—pain—comfort. The sequence may be repeated for weeks or months; then there may be a period of freedom, only to be followed by another attack. Hemorrhage, perforation, and obstruction due to pyloric stenosis are important complications.

**Lesions.**—It is not easy to determine the true *relative frequency* of chronic gastric ulcer as compared with duodenal ulcer. Surgical statistics show that chronic ulcer is much commoner in the duodenum. In the Toronto General Hospital out of 875 cases of chronic ulcer coming to operation 70 per cent were in the duodenum and 30 per cent in the stomach. It must be remembered, however, that the surgeon sees a special class of cases, those in which symptoms of obstruction form a prominent feature. In the autopsy material of the same hospital gastric ulcers were nearly twice as common as

duodenal. On the other hand Hurst and Stewart found duodenal ulcers somewhat more frequent in their autopsy material.

The *sex incidence* of peptic ulcer has shown a notable change during the past half century. In the earlier part of this period Alsted found that in Denmark the incidence of males to females was 1 to 5; by the beginning of the century it was 1 to 1; in the decade from 1920 to 1930 it had risen to 3 to 1. This is due to the increased frequency of duodenal ulcer, which is commoner in the male. *Acute* ulcers may occur in any part of the stomach. They are usually shallow, more of the nature of erosions, but occasionally they may perforate the whole thickness of the wall. The *chronic* peptic ulcer is much more localized. Duodenal ulcers are practically always limited to the first part of the duodenum, usually on the anterior wall so that perforation is relatively common, as the ulcer in this position cannot become adherent to the abdominal wall. The vast majority of ulcers occur along the line of the lesser curvature or in close proximity to it. It is rare in the region of the cardia, in the fundus and on the greater curvature, and is uncommon in the pyloric canal (about 1 inch in length). The site of election is between 2 and 4 inches from the pylorus, whereas cancer is commonest in the juxtapyloric portion. Sometimes the ulcer is placed astride the lesser curvature (*saddle-shaped ulcer*). When such an ulcer heals the stomach will be divided into two parts, a condition known as *hour-glass stomach*. The fundus glands produce acid, whereas the glands in the pyloric (large) and cardiac (small) zones do not. The line between the acid and non-acid-producing areas is known as the acid line. The zone of pyloric glands, and therefore the acid line, reaches much higher on the lesser than on the greater curvature. The line varies considerably in position in different stomachs, and can readily be determined by opening the stomach along the greater curvature and taking blocks of tissue along the lesser curvature.

Peptic ulcers do not arise in the area of acid production. They are formed immediately on the pyloric side of the varying acid line. It is of particular interest to note that peptic ulcers in Meckel's diverticulum are situated in the intestinal type of mucosa, not the heterotopic acid-producing mucosa.

The *gastric ulcer* is usually single but may be multiple (5 to 10 per cent). It is shaped like a funnel, penetrating the muscular coat sometimes as far as the peritoneal surface. (Fig. 233.) Small ulcers tend to be circular and larger ones oval. The sides are generally sloping but may be steep; the cardiac side of the ulcer is steeper than the pyloric. The edge is raised, often overhanging, and the floor is hard and indurated. The larger the ulcer, the more likely is it to be malignant. Most simple ulcers are less than 1 inch in diameter, but some may attain a much larger size. On the peritoneal surface the presence of the ulcer is indicated by pallor and well-marked induration so that it can be felt better than seen.

A *duodenal ulcer* situated in the first part of the duodenum, or more specifically the duodenal bulb (pyloric cap), is usually small and

## PLATE XI



### Chronic Peptic Ulcer

Both the muscularis mucosae and the muscular coat are replaced by scar tissue. (Aniline blue connective-tissue stain.)



associated with marked cicatricial contraction, so that small diverticula are often formed between the ulcer and the pylorus. In very chronic and especially in healed ulcers cicatricial contraction may shorten the distance between the pylorus and the papilla from the normal 8 to 6.5 cm. or less.

*Microscopically* in well-fixed surgical material four zones can be distinguished in the floor of the ulcer (Fig. 234): (1) an inflammatory zone consisting of fibrin and polymorphonuclear leucocytes; (2) a zone of necrotic



FIG. 233.—Peptic ulcer. This is a characteristic example of an innocent ulcer of the stomach.



FIG. 234.—Peptic ulcer showing zones of necrosis, granulation tissue, and fibrosis  $\times 200$ .

granulation tissue; (3) a zone of living granulation tissues; (4) a zone of dense scar tissue which forms one of the most important features of the ulcer. (Plate XI.) It extends in the submucosa for some distance under the intact mucous membrane, and materially interferes with healing in preventing the approximation of the edges. (Fig. 235.) When a chronic peptic ulcer reaches a certain stage it simply cannot heal. There is nearly always greater destruction of the muscular coat than of the mucosa. Evidence of active inflammation in the shape of dilated vessels and foci of chronic inflammatory cells can be seen even in the most quiescent scar tissue, showing that irritation is still going on. The vessels are often narrowed by very marked endarteritis obliterans. At the *margin* of the ulcer there may be evidence of epithelial pro-

liferation in the form of downgrowths, and glandular tissue may be found beneath the muscularis mucosæ. These changes are apt to be wrongly interpreted as indicating carcinoma.

**Healing.**—Acute ulcers and erosions heal rapidly and easily. Chronic ulcers may also heal though with difficulty. It appears likely from logical evidence that an ulcer may heal, recur, break down, and heal again, with each recurrence becoming deeper and more fibrotic. Healing is interfered with by (1) the acid gastric juice, (2) the necrotic layer on the base which covers the granulation tissue and provides no footing for the ingrowing epithelium, and (3) the dense scar tissue which prevents approximation of the edges. It is difficult to study the healing process in human material, but Mann has given us an excellent



FIG. 235.—Peptic ulcer. The submucosa is extensively fibrosed. There are large collections of inflammatory cells far below the surface of the ulcer.

study of the process in experimental ulcers. When the experimental ulcer (which is chronic in type) is protected from the acid gastric juice by gastro-enterostomy the base becomes clean in a few days, the mucosa starts to grow in from the edges in ten days, and by the end of a month it is almost impossible to find the site of the lesion, the hard and indurated base having become quite soft and thin. *Microscopically* the leucocytes and necrotic tissue disappear, the ulcer becomes filled with healthy granulation tissue, over which the mucosa grows as a single layer of flat cells which later become typically columnar and form tubular glands. The young mucosal cells are at first very fragile and easily destroyed by the passage of gastric contents over the ulcer.



**The Relation of Symptoms to Lesions.**—The great symptom is *pain*, relieved by the taking of food and alkalis. It is when the stomach is empty that the pain is most severe, so that the patient may have to get up in the middle of the night to eat a biscuit or drink a glass of milk. There are two possible explanations of the pain, both of which have warm supporters. (1) It may be due to the acid gastric juice acting on the raw surface of the ulcer. As the acidity is neutralized by food or alkalis the pain becomes relieved. When the ulcer becomes perforating the pain is no longer relieved by alkalis. (2) The pain may be muscular in nature and unconnected with the action of the acid juice on the ulcer. The inflammatory foci in the muscularis give rise to contractions in the neighborhood of the ulcer and especially at the pylorus. These increase the intragastric pressure and the tension of the muscle fibers, and this increase is reflected in the sensation of pain.

A patient may present a typical history of peptic ulcer, yet operation may reveal no lesion in the stomach or duodenum. These organs receive the same double nerve supply (sympathetic and parasympathetic) as the other abdominal organs, and the possibility of reflected painful sensations must be borne in mind. The stomach is like a sensitive receiving set which tunes in to distant stations; at the same time it is a loud speaker which amplifies any notes of distress it may receive. Not only may all the symptoms of ulcer be present without an ulcer, but a well-developed ulcer may be present without symptoms. These facts do not make the task of explaining the clinical picture any easier.

The other symptoms are rather in the nature of complications. *Hemorrhage* is very common. It is due to erosion of a vessel in the floor of the ulcer. If the hemorrhage is severe the blood will be vomited; when the blood has been retained in the stomach and altered by digestion the vomitus will have a brown (coffee-ground) appearance. If the hemorrhage is slight it may only be detected in the form of occult blood in the stools. Minute erosions may cause oozing of blood from the mucosa (gastrostaxis). *Perforation* is more likely to occur in ulcers with a very short history in which there is rapid penetration of the muscular wall. In ulcers of long standing there are likely to be adhesions between the ulcer on the posterior wall of the stomach and such organs as the liver and pancreas. As duodenal ulcer is commoner on the anterior than the posterior wall, perforation is more likely to occur in this form of peptic ulcer. *Cicatricial contraction* at the pylorus will cause pyloric stenosis and great dilatation of the stomach. If the ulcer is on the lesser curvature the scar tissue may pull upon the greater curvature causing the constriction characteristic of hour-glass stomach.

**Malignant Change in Gastric Ulcer.**—On this important question much difference of opinion exists. The matter is important because the outlook on treatment (medical or surgical) is so much influenced by the answer to the question. Some observers consider that the majority of simple ulcers show microscopic evidence of malignant change. Others give as low a figure as 5 per cent. There is no doubt that a chronic peptic ulcer *may* become carcinomatous, just as an ulcer in any part of the body may undergo malignant change. The important question is, *how often* does this occur? The difference of opinion depends largely on different interpretations of the microscopic appearance. To one pathologist the presence of isolated abnormal epithelial cells and aberrant tubules in the neighborhood of a tumor spells carcinoma, while to another they are the result of distortion produced by the contracting fibrous tissue or merely part of the regenerative process. In examining a malignant ulcer the following points would be in favor of it representing a malignant change in a peptic ulcer:

(1) the edge is carcinomatous but not the base, for the latter is densely fibrous and resists invasion by carcinoma cells; (2) marked endarteritis; (3) complete destruction of the muscular coat and its replacement by fibrous tissue; (4) fusion of the muscularis mucosæ and the muscular coat at the margin of the ulcer due to healing.

The site of election of the lesion suggests that malignant change is not of common occurrence. The majority of cancers are situated at the pylorus, whereas the majority of ulcers are from 2 to 4 inches from the pylorus.

The clinical evidence is as important as the pathological. The true ulcer cases have a history of many years' duration, whereas in cancer there is usually a history of only a few months' gastric disturbance, the patient often remarking that previously he was "able to digest nails." If cancer were often preceded by ulcer the reverse would be the case. Finally, ulcer of the duodenum is very common and cancer of the duodenum is extremely rare. Occasionally the symptoms of ulcer may change into those of cancer, the pain becoming continuous and losing its relation to food. The most reasonable figures appear to be as follows: about 5 per cent of chronic gastric ulcers become malignant, while about 20 per cent of gastric cancers arise from a preëxisting ulcer.

**Secondary Jejunal Ulcer.**—After the operation of gastro-enterostomy for peptic ulcer a secondary ulcer may develop at the gastro-jejunal junction or in the efferent loop of the jejunum within a few inches of the opening (stoma ulcer). This has all the characters of a peptic ulcer. It is caused by the unaccustomed action of the acid gastric juice on the mucosa of the jejunum, together with some accessory factor such as local injury of the mucosa due to the presence of an unabsorbable suture.

## TUMORS OF THE STOMACH

**Cancer of the Stomach.**—Carcinoma of the stomach is the commonest form of malignant disease affecting the internal organs. In Great Britain it is nearly three times as common as cancer of the uterus and twice as common as cancer of the breast. Moreover, on account of its remarkable silence the cure-rate is the worst in malignant disease. About one-half of human cancers occur in the alimentary canal. Such cancers are very rare in all other series of animals. Thus in 142,000 mice only 15 had cancer of the stomach at autopsy (Wells). It is moreover impossible to produce gastric carcinoma experimentally by means of the various carcinogenic agents which are so potent a means of producing tumors in other sites. The disease is much more frequent in the poorer classes than among the well-to-do. Thus in England it is three times commoner amongst the poor. The geographic incidence is also of interest. In Britain the incidence is 22 per cent of all cancers in men, in America 42 per cent, in Holland 55 per cent, in Czechoslovakia 66 per cent. These differences are probably due to different habits in eating, drinking and chewing tobacco, possibly also to dental hygiene. All of these may lead to chronic gastritis, which is probably

a precancerous condition of importance. It may be noted that the incidence is high among stokers and barmen, but low among clergymen. Perhaps the most remarkable fact in the geographic pathology of gastric carcinoma is the almost complete absence of the disease amongst the Malays of Java and Sumatra, whereas primary cancer of the liver heads the list of malignant disease amongst these people (Bonne). Gastric ulcer is equally rare. On the other hand amongst the Chinese of these islands both gastric cancer and gastric ulcer are common, although surpassed in this respect by cancer of the liver. The usual age period is about sixty, but it may occur much earlier. The common site is the pyloric region. About 60 per cent occur in this position, 20 per cent along the lesser curvature and at the cardiac end, while most of the remaining 20 per cent are along the greater curvature. This distribution should be compared with that of peptic ulcer. The question of the relation of carcinoma to simple ulcer has already been discussed. About 5 per cent of chronic gastric ulcers may develop into carcinoma.

**Symptoms.**—The chief symptoms are dyspepsia in a man in the cancer age period who has previously had a good digestion, loss of appetite, with pain as a late manifestation. The gastric contents show absence of free hydrochloric, presence of lactic acid and blood. Loss of weight and marked anemia are among the general symptoms.

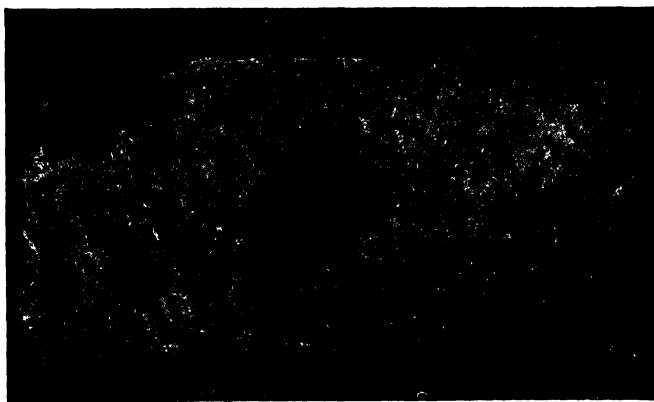


FIG. 236.—Polypoid form of carcinoma of stomach. (Boyd's Surgical Pathology.)

**Lesions.**—The *gross appearance* varies greatly. (1) The tumor may form a large, soft, fungating mass which projects into the lumen of the stomach like a mushroom. Ulceration of the surface gives rise to infection and hemorrhage. This may be called the *papillary form*. (Fig. 236.) (2) More often the tumor is only slightly elevated and early becomes ulcerated. The edges of the ulcer are raised and rounded, and its diameter may be much greater (above 2.5 cm.) than that of the usual peptic ulcer, although there are exceptions to this rule. This variety is the *excavating form*. (Fig. 237.) A simple ulcer which

becomes malignant belongs to this group. The cut surface shows marked thickening of the wall with yellow flecks of necrosis, and sometimes nodules on the serous surface. (3) The *diffuse infiltrating form*,



FIG. 237.—Excavating carcinoma of stomach. (Boyd's Surgical Pathology.)

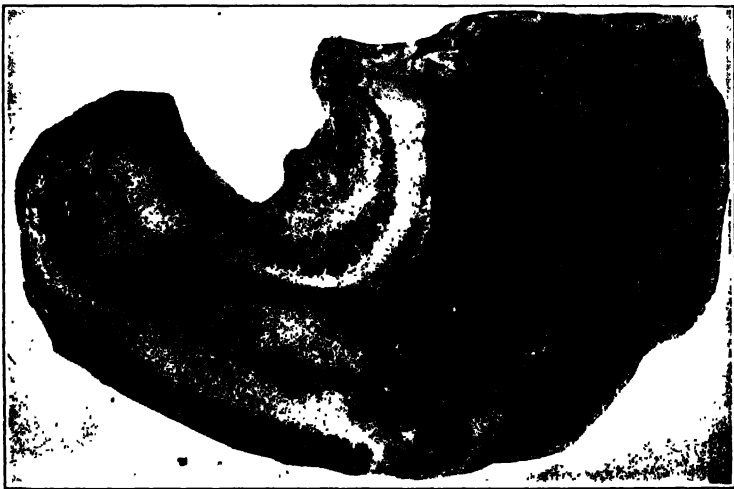


FIG. 238.—Carcinoma of the stomach. This is an example of the local pyloric form of the infiltrating variety.

in which no real tumor is seen but a great thickening of the stomach wall. This may be local or diffuse. The *local* form occurs at the pylorus, where there is a dense ring of sclerotic tissue which causes

great pyloric stenosis and marked dilatation of the stomach. (Fig. 238.) The cut surface is greatly thickened and densely hard. The *diffuse* variety is known as *linitis plastica*, cirrhosis of the stomach, and leather-bottle stomach. The entire stomach is involved; it is very small and very thick-walled. The normal stomach is about 12 inches long and contains 40 ounces; the leather-bottle stomach may only measure 4 inches and contain only 4 ounces. The wall may be an inch thick. The walls of the stomach are peculiarly stiff and rigid. There is no ulceration of the surface, but the mucosa is firmly tacked down to the underlying muscular coat. The stomach is involved from the cardia to the fundus; the thickening stops abruptly at the pyloric ring and does not invade the duodenum. In the diffuse form it may be very difficult to demonstrate any cancer cells, most of which seem to die out, so that the condition is of low malignancy.

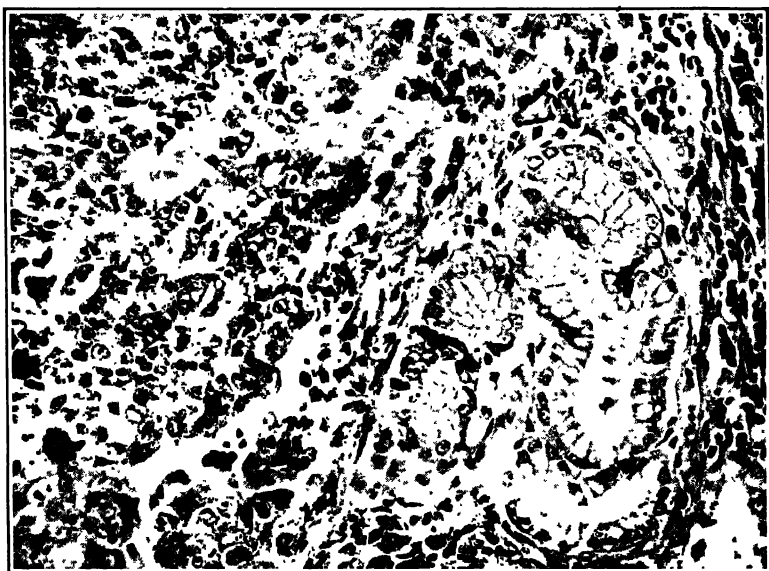


FIG. 239.—Carcinoma of stomach. The rudimentary glands to the left are highly malignant in type.  $\times 300$ .

The *microscopic appearance* varies considerably. Although the stomach is a glandular organ, cancer frequently fails to form even rudimentary glands. The cells are usually arranged in cords or masses, or seen as isolated cells. This is in marked contrast to cancer of the bowel, in which an adenomatous arrangement is nearly always well marked. The polypoid (less malignant) form is likely to show the best examples of glandular arrangement. (Fig. 239.) The normal mucosa is replaced by atypical glandular tubules which penetrate the muscularis mucosæ, spread widely in the submucous coat, and may finally appear on the serous surface. The glands are lined by one or

several layers of cells with large hyperchromatic nuclei so that the tubules appear much darker than the surrounding normal ones. In other cases the tumor is more anaplastic, glandular acini are poorly formed or completely absent, and the cancer cells are arranged in masses or in single columns separated by a dense stroma of the scirrhous type. Such a picture is more likely to be seen in ulcerocarcinoma. The most extreme anaplasia is met with in the diffuse infiltrating variety, but in spite of the anaplasia the tumor is not of a high grade of malignancy. Here there is no attempt at gland formation, and the individual cells or clumps of cells are lost in a scar-like stroma so dense that it appears to be strangling them. Many of the cancer cells contain droplets of mucin which can be stained red with Best's carmine stain, a valuable method of identifying malignant cells embedded in dense fibrous tissue. When the mucin production is excessive the tumor is converted into a soft gelatinous mass; this variety is called *mucoid carcinoma*, formerly known as colloid cancer, and forms about 5 per cent of gastric carcinomas. The cells are distended and finally destroyed by clear mucinous material, but clumps of recognizable carcinoma cells are found here and there. The change does not affect the prognosis.

*Gastritis and Carcinoma.*—The mucous membrane not only in the immediate neighborhood of the tumor but also at a distance may show chronic gastritis, either atrophic or hyperplastic, with atrophy of the peptic cells and tubules, and a transformation of the gastric into the intestinal type of cells with many goblet cells. The changes are associated with an early diminution or disappearance of the hydrochloric acid in the gastric juice. The gastritis, which is much more evident in surgical than in autopsy material, may be regarded as a precancerous condition, and by some these changes are believed invariably to precede carcinoma. In other words, carcinoma does not originate in a normal stomach.

*Spread.*—Cancer of the stomach spreads locally, to the lymph nodes, and to distant organs. (1) *Local spread* occurs both in the stomach wall and to neighboring organs. Spread in the stomach wall takes place mainly in the loose submucous coat. In the diffuse infiltrating form the entire submucosa is first infiltrated and then becomes fibrosed. The tumor may penetrate the entire thickness of the wall and appear on the serous surface, from which the tumor cells may be spread by implantation over the abdomen (peritoneum, omentum, ovaries). The duodenum is never invaded, the tumor stopping short at the pylorus. Spread to neighboring organs usually involves the liver or the pancreas when the cancer is on the posterior wall of the stomach. (2) *Spread to the lymph nodes* is extremely common. At first the regional nodes draining the stomach are affected, but there may be distant spread along the thoracic duct, and the supraclavicular and cervical glands may be enlarged, especially on the left side. (3) *Spread to distant organs* is by the blood stream. The liver is involved first and most frequently *via* the portal vein. It may be enormously enlarged

though the gastric tumor may be too small to be detected clinically. There may be blood spread to the lungs, central nervous system, kidneys and bones. The abdominal organs, especially the ovaries, may be infected by implantation from a tumor which has perforated the serous coat.

**Prognosis.**—As with other forms of cancer, this depends on early diagnosis. The outlook is not so unfavorable as is commonly believed, and is steadily becoming less so. Of 10,000 patients at the Mayo clinic who survived resection of the stomach between 1907 and 1938 29 per cent were alive at the end of five years, after which the chance of survival was about the same as for persons of comparable age in the general population (Walters *et al.*).

**The Relation of Symptoms to Lesions.**—*Pain* as an early symptom is unfortunately absent in about one-half the cases of cancer of the stomach, for it depends on destruction and irritation of the muscular coat; quiet infiltration by tumor cells may cause little irritation. Pain is likely to be present in ulcerocarcinoma, and when the tumor is at the pylorus where it excites spasm. If the pain of chronic peptic ulcer in a man in the cancer age changes its character, becomes continuous, and loses its relation to food, a malignant change is probably taking place. *Loss of appetite* and a sense of satiety before the meal is finished are due to the carcinomatous infiltration of the muscular coat interfering with the healthy tonus upon which the sensation of hunger depends. (Fig. 240.) *Absence of free hydrochloric acid* in the stomach contents is due partly to the destruction of the mucous membrane by the tumor, partly to secondary changes which develop in the rest of the mucosa leading to atrophy of the oxyntic cells. The suppression of hydrochloric acid is not so constant or complete as in pernicious anemia. In early carcinoma free hydrochloric acid is often present, and it can be demonstrated by the fractional method in about one-half the operable cases. *Lactic acid* appears as the result of pyloric obstruction and the decomposition of retained food. *Blood* in the stool (occult blood) is a most important and constant sign; it is due to ulceration and will therefore be absent in the diffuse infiltrating form. It can also be found in the stomach contents. *Fragments of tumor* may be found in the stomach washings. *Anemia* is very common. It is usually of the secondary type, but is occasionally indistinguishable from pernicious anemia except that the icterus index (bilirubin in the blood) is not above normal. The anemia may be due partly to continued loss of blood, partly to ulceration and sepsis, but the more primary form may well be due to that loss of the power of the stomach to produce the hematopoietic principle (stored later in the liver) which is responsible for pernicious anemia.

**Cancer of the Duodenum.**—Although simple ulcer is so common, carcinoma is rare in the duodenum, but in my experience not so rare as is commonly stated.



FIG. 240.—Carcinomatous invasion of the muscular wall of the stomach. It is this infiltration which destroys the muscle tone and is responsible for the loss of appetite.  $\times 175$ .

The usual site is the second part, not the first part as in ulcer. The tumor causes obstruction of the biliary and pancreatic ducts. It is easy to mistake cancer of the head of the pancreas for cancer of the second part of the duodenum.

**Sarcoma.**—This is a rare tumor which forms a large polypoid mass that projects into the stomach. It usually arises from the muscle, so that it is a myosarcoma made up of elongated cells. In lymphosarcoma and Hodgkin's disease there may be local lesions in the gastric mucosa.

**Innocent Tumors.**—These also are rare. The commonest is a *myoma* arising from the muscle fibers and forming a mass in the cavity of the stomach like a submucous fibroid of the uterus. Fibroma, lipoma and hemangioma have been described. *Multiple adenomata* or *diffuse gastric polyposis* is a condition in which soft polypoid masses are scattered over the surface of the mucous membrane or are arranged in a group. The microscopic structure shows an adenomatous formation of new glands. Occasionally one of the adenomata may become malignant. Severe anemia and achylia gastrica are common symptoms.

**Adenomyoma** is a rare and peculiar lesion which is confined to the pyloric end of the stomach, but may also occur in the duodenum and jejunum. Forming a localized yellowish nodule in the wall of the stomach (where it may be mistaken for carcinoma) or bowel, it really appears to be a benign neoplasm arising from heterotopic epithelium. It consists of a mixture of pyloric or duodenal (Brunner's) glands and pancreatic tissue arranged in nodules which are surrounded by plain muscle. The lesion is of clinical significance, as it may cause gastric symptoms.

**Tuberculosis.** This is rare, and is secondary to tuberculosis elsewhere, usually in the lung. The usual lesion is an ulcer, single or multiple, with undermined edges. There may be a lump instead of an ulcer, and sometimes merely a scar. Microscopic examination may reveal tuberculosis in a lesion which has been mistaken for a peptic ulcer or cancer.

**Syphilis.**—Syphilis of the stomach is probably quite rare, although frequently diagnosed by some clinicians from the roentgen-ray picture and a positive Wassermann reaction. In 13,000 autopsies at the London Hospital Turnbull was unable to find a single undoubted case. The disease begins as a gumma which breaks down and forms an ulcer. This is likely to be large and the edge is hard and raised, so that it is easily mistaken for a carcinomatous ulcer. The *microscopic* changes are those characteristic of syphilis, *i. e.*, infiltration with plasma cells, lymphocytes and eosinophils, endarteritis obliterans and marked fibrosis. It must be remembered that any of these changes may be found in the base of a simple peptic ulcer, so that the only incontrovertible proof that the ulcer is syphilitic is the finding of the *Spirochæta pallida* either in sections or by animal inoculation.

### POSTMORTEM DIGESTION

No organ shows postmortem change so quickly as the stomach, because after death the anti-enzymes disappear which prevent the gastric juice from acting on the stomach wall during life. There may be mere softening of the mucosa at the cardiac end so that it can be scraped off, or the gastric juice may eat a hole in the stomach wall at the cardiac end and sometimes in the diaphragm, so that gastric contents are found in the abdominal and pleural cavities. To distinguish this from an antemortem condition (which may be of importance in suspected foul play), the edges of the opening are examined microscopically for evidence of reaction, which of course is absent if the lesion is a postmortem one.



### CONGENITAL PYLORIC STENOSIS

This is a condition of congenital hypertrophy of the pylorus usually occurring in male breast-fed infants. The pylorus is greatly thickened so that it projects into the duodenum. The thickening extends for a few centimeters along the pyloric canal, then gradually disappears. The pyloric opening is greatly narrowed and is filled with closely-packed folds of mucous membrane. The thickening is caused by an enormous hypertrophy of the circular layer of muscle fibers. An element of spasm seems to be added to the hypertrophy, because the persistent vomiting which is the principal symptom of the stenosis does not begin for a week or two. The thickened pylorus can often be felt as a round firm mass. Surgery offers no more dramatic result than in the case of the Fredet-Rammstedt operation, which consists in dividing the hypertrophied muscle down to the mucosa; the vomiting stops as if by magic, and the starved child at once begins to put on weight.

### ACUTE DILATATION OF THE STOMACH

After an abdominal operation under general anesthesia the stomach may occasionally become very rapidly distended until it reaches an enormous size. The condition is likely to be fatal unless treated promptly. At autopsy the stomach may fill the greater part of the abdomen, its wall is very thin, and it contains a very large amount of fluid, although in the early stages the contents are entirely gaseous. The dilatation may stop at the pylorus or may extend as far as the point where the third part of the duodenum is crossed by the superior mesenteric vessels. It is probable that there are two etiological factors: (1) reflex atony of the stomach wall produced by trauma to the abdominal organs similar to the paralysis of the bladder, which may follow operations on the perineum; (2) swallowing of air while the patient is under the anesthetic. In the later stages there is a great outpouring of water fluid known as gastric succorhea. The use of the stomach tube in the early stage soon relieves the condition.

### CHRONIC DUODENAL ILEUS

Chronic ileus (obstruction) of the duodenum may be caused by narrowing of the angle between the superior mesenteric artery and the aorta through which the third part of the duodenum has to pass. Pressure on the duodenum is produced by the downward pull of the small intestine if it hangs over the brim of the pelvis without resting on the floor of the pelvis. The duodenum may be extremely dilated and its wall thickened. The intestine beyond the obstruction is collapsed. In some cases the stomach may share in the dilatation.

**Duodenitis.**—Inflammation of the duodenum without ulceration appears to be a distinct entity. Although there is no mucosal defect, the submucosa and muscularis are infiltrated with leucocytes and lymphocytes, and show congestion and edema. Similar lesions are found in the neighborhood of a chronic ulcer. The serosal surface is congested and may be stippled. The symptoms are often similar to those of ulcer, and there may even be hemorrhage. The lesion may involve the ampulla of Vater and obstruct the passage of bile into the duodenum, thus producing an obstructive jaundice which may easily be mistaken for that caused by cancer of the head of the pancreas.

## DUODENAL DIVERTICULA

Roentgen-ray studies have shown that diverticula of the duodenum are much commoner than used to be thought. Two types may be recognized, primary and secondary. A *primary* diverticulum usually arises from the second part of the duodenum, sometimes from the first part, rarely from the third part. It springs from the inner and posterior aspect of the bowel along the line of entrance of the vessels which weaken the wall. There is a herniation of the mucosa through the muscular coat, and the sac thus formed may be as small as a pea or as large as a plum. It may be single or multiple. It occurs in middle and late life. Often discovered accidentally, it may give rise to no symptoms, but when large it may cause dyspepsia, probably from pressure. *Secondary* diverticula are secondary to a duodenal ulcer, so that they occur in the first part of the duodenum. There may be bulging of one or both sides of a healed scar due to traction. The condition is of no clinical significance.

## ADDITIONAL READING

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## CHAPTER XX

### THE INTESTINES

#### ENTERITIS

**ENTERITIS** means inflammation of the intestine (*enteron*, intestine). The term may be used in this sense, but as colitis signifies inflammation of the large bowel, enteritis is often limited to inflammation of the small bowel. Enteritis is usually a catarrhal inflammation. It may be ulcerative. The term membranous or diphtheritic inflammation is applied to those cases in which a definite layer of necrotic mucosa and fibrin is formed.

Acute enteritis may be produced by: (1) indigestible and irritating foods, (2) food poisoning, and (3) chemical poisons. So-called food poisoning is really due to the action of pathogenic bacteria contained in the decomposing food, the most important being *Bacillus enteritidis* (Gärtner) and the paratyphoid group. Many chemical poisons may irritate the intestine. Arsenic and mercury cause inflammation of the lower part of the ileum and most of the large bowel, apparently being excreted lower down after having been absorbed. In infective fevers, septicemia, and uremia enteritis may be present.

**Lesions.**—The mucous membrane is swollen, edematous, covered with a slimy exudate, and flecked with red spots. It is seldom red throughout except in the severe inflammation produced by chemical poisons. The lymphoid follicles, particularly in children, are often swollen and the overlying mucosa may be shed off so as to form little, clear-cut, shallow ulcers (follicular ulcers). *Microscopically* the change is confined to the mucosa and submucosa which are infiltrated with round cells and show marked edema. Polymorphonuclears are present in the more acute stages. The surface epithelium is degenerated, but in the intestine as in the stomach it is always difficult to separate antemortem from postmortem degenerative changes.

#### BACILLARY DYSENTERY

Bacillary dysentery and amoebic dysentery are two entirely different diseases, and the only justification for grouping them under one heading is historical usage. Bacillary dysentery is very common in tropical countries, but is also found in the temperate zone, especially where men are crowded together under poor hygienic conditions. It is thus a great destroyer of armies in the field, it appears in large mental hospitals in both endemic and epidemic form, and it is the chief cause of the acute enteritis of children associated with the passage of pus and blood.

**Bacteriology.**—The dysentery bacillus belongs to the coliform group, being Gram-negative but non-motile. There are several varieties

which can be grouped into two main classes, the Shiga group and the Flexner group. The Shiga bacillus is a non-mannite fermenter, and produces both an exotoxin and an endotoxin upon the intestinal mucosa. The Flexner form produces no exotoxin, and its endotoxin is not very potent. The two forms of infection can be differentiated by testing the agglutinating power of specific Shiga and Flexner antisera against the organisms isolated from the feces. By the end of a week the patient's blood develops specific agglutinins, so that by testing the serum against the two cultures the form of infection can be determined.

**Symptoms.**—Dysentery is a diarrhea characterized by the presence of mucus, pus, and blood in the stools (a "bloody flux"), and accompanied by straining and tenesmus. The infection is an acute one lasting several weeks, but the condition may become chronic or there may be periodic recurrences. In addition to the local symptoms the patient shows evidence of the action of a powerful diffusible toxin and dies of toxemia.

**Lesions.**—Bacillary dysentery resembles diphtheria in that the bacilli remain localized, do not penetrate the tissues at first nor invade the blood stream, and produce local necrosis and distant damage by the means of their exotoxins. When an ulcer has been produced the bacilli may penetrate into the deeper parts of the wall. The disease is an acute colitis, but the lower part of the ileum may also be involved. The toxins cause an acute inflammation of the wall of the bowel, patches of the mucous membrane become necrotic, are converted into sloughs, and when these separate, ulcers are formed. The surface of the ulcer may become covered by an inflammatory exudate consisting of fibrin and polymorphonuclear leucocytes which, together with the necrotic material, may form a false membrane (diphtheritic inflammation). The ulcers seldom penetrate the muscularis mucosæ, but sometimes they may reach the serous coat and perforate. The ulcers are clear cut, and have not the undermined edges seen in the amoebic form. There may be many small ulcers, or they may coalesce to form a few very large ones. The mucosa between the ulcers may become papillomatous.

*Microscopically* the wall of the bowel is infiltrated with polymorphonuclear leucocytes. There is marked edema and thickening of the submucosa. Large numbers of bacilli are present in the floor of the ulcer. *Healing* takes place by the formation of granulation tissue which becomes covered by a simple epithelium without glands. If the ulceration is superficial there is little scarring, but when deep there may be much scar formation with the production of marked stenosis of the bowel.

**The Relation of Symptoms to Lesions.**—The pain, tenesmus, and diarrhea are due to the acute inflammation of the large bowel. The pus and blood in the stools are the result of the ulceration. Mucus may be abundant, especially in the chronic cases. As the disease is a local one there are no signs of septicæmia, such as acute splenic swelling. The toxins may act on the nervous system, producing a peripheral neuritis, and on the joints causing a painful effusion. Liver abscesses are very rare (cf. Amoebic dysentery).

**AMOEBIĆ DYSENTERY**

The amœbic form of dysentery is caused by *Entamœba histolytica*, a protozoal parasite. It is more gradual in onset and more protracted in its course than the bacillary form, sometimes lasting for months or years. The incubation period varies from ten to ninety days. Although primarily a disease of the tropics there is a growing incidence of infestation with the parasite in temperate regions, and serious localized epidemics are becoming more common. These can usually be traced to cooks and other handlers of food (in hotels, etc.) who are either carriers of the amœba or suffer from the disease in a mild form. An infected water supply is another source of danger. A remarkable outbreak occurred in Chicago, June 1933–June 1934, during which period there were 1409 cases (98 deaths), 75 per cent of whom had contact with one or other of two hotels. From this center the disease was scattered over 400 cities, 43 states and 3 Canadian provinces. At first it was thought to be a carrier epidemic, as the incidence of carriers among the employees of the two hotels was 37.8 and 47.4 per cent, but eventually it was traced to water infection, an overhead sewer leaking into the drinking water supply. The parasite may be present in two forms, one active or amœboid (trophozoite), the other encysted. The latter is developed when conditions for growth are not favorable, and is the only infective form, for the active form is destroyed by the HCl as it passes through the stomach. The cysts may live outside the body for weeks in moisture and shade. The active form is detected by direct microscopic examination of a warm stool preparation, but the cysts are shown up best when such a preparation is stained with a mixture of iodine and eosin. The cysts do not occur in the tissues, nor are they passed in any numbers in the acute dysenteric stage (diarrhea); they are generally found only in semiformed or formed stools. For doubtful encysted forms a fixed smear should be stained with iron hematoxylin. In acute cases the stool contains the active form, while in chronic cases and carriers cysts are to be expected. The features by which the two forms may be recognized are described in Chapter VIII.

**Lesions.**—When a cyst is swallowed in food or water it breaks up in the lower part of the small bowel and liberates a single amœba with 4 nuclei. These divide into 8, and 8 small amœbæ are found. When they reach the large bowel they penetrate the lumen of the glands and, destroying the epithelium with which they come in contact by proteolytic enzymes, they penetrate the deeper tissues. No lesion is produced in the bowel unless the amœbæ colonize actively; they merely enter the portal venules and to a lesser extent the lymphatics. If they colonize in the submucosa, the result is dysentery. The parasites spread out in this coat and set up a colliquative necrosis by virtue of the proteolytic ferment which they produce. All this is quite different from bacillary dysentery where the organisms remain on the surface and by means of their diffusible toxins excite a suppurative

inflammation instead of a quiet necrosis in the underlying tissue. The mucosa overlying the necrotic area also dies and is cast off as a slough, so that ragged ulcers are formed. These ulcers have deeply undermined edges, because the submucosa is more extensively involved than the mucosa. The mucosa between the ulcers appears remarkably healthy because no diffusible toxin is at work. The ulcers are deeper than in the bacillary form, and the floor is often formed by the thickened peritoneum.

The *microscopic picture* is one of quiet necrosis with little or no inflammation. Large numbers of amœbæ can be seen in the wall of the bowel. They digest the surrounding tissue by means of their proteolytic ferment, so that they frequently lie in small spaces (Fig. 241), but they appear to excite comparatively little reaction. Any inflammatory cells in the floor of the ulcer are mononuclear in type. At a later date secondary infection may occur and this may cause some suppuration. The amœbæ penetrate the portal venules and can be seen lying within the lumen, so that they readily pass to the liver.

*Liver abscess* is thus a common complication of amœbic dysentery. Although the lesion is commonly known as solitary abscess, it is multiple in over 50 per cent of the cases, being more frequent in the right lobe. There may be a few large or numerous small abscesses. The lesions are really not true abscesses, but are formed by the liquefaction necrosis of the liver cells produced by the digestive ferment of the amœbæ. The abscess may rupture into the abdominal cavity, or through the diaphragm into the lung, the patient expectorating a brown "anchovy sauce" material containing many amœbæ.



FIG. 241.—*Amœba histolytica* in wall of bowel.  $\times 400$ .

#### **Bacillary and Amœbic Dysentery Compared.**

—The chief symptom of dysentery—diarrhea with blood, mucus and pus in the stools—is the same in both forms. Bacteriological and immunological tests are of value in differentiating the two forms, but a rapid and useful method is the cytological examination of the stools, the type of cell depending on the histological reaction in the lesions. It will be remembered that there are three types of necrosis: lysis, pyknosis, and karyorrhexis. In *bacillary* infections cellular lysis is marked, the result being "ghost cells" from the macrophages and "ring nuclei" from the polymorphonuclear leucocytes. About 90 per cent of the cells are polymorphonuclears, but this loses its value from the fact that when amœbic lesions become secondarily infected the exudates may be purulent. The most important cells are the macrophages and their ghost forms. Unfortunately these may bear a striking resemblance to amœbæ, and

be a cause of mistaken diagnosis except in the hands of an expert, as happened in the epidemics both at Gallipoli and on Corregidor. In pure amœbic infections the cells are few in number and are mainly mononuclears. They present either a "mouse-eaten" appearance due to the action of the digestive enzyme on parts of the cytoplasm, or "pyknotic bodies" from the nuclear fragments. Large numbers of red blood cells are always present in addition to the amœbæ. Charcot-Leyden crystals are characteristic of amœbic dysentery, and are not found in the bacillary form.

Some of the principal points in which bacillary differs from amœbic dysentery are summarized as follows:

	<i>Bacillary dysentery</i>	<i>Amœbic dysentery</i>
1. Type of lesion	Suppurative	Necrotic
2. Depth of ulcer	Generally shallow	Generally deep
3. Edge of ulcer	Sharp	Undermined
4. Intervening mucosa	Inflamed	Normal
5. Organisms in lesions	Bacillus dysenteriae	Entamoeba histolytica
6. Cytology of stools	Polymorphonuclears	Mononuclears
7. Liver abscess	Rare	Common

### IDIOPATHIC ULCERATIVE COLITIS

Bacillary and amœbic dysentery are comparative rarities in civilian practice in non-tropical countries. Cases with symptoms of dysentery and ulcerative lesions in the large bowel but in which there is no evidence of infection with *B. dysenteriae* or *E. histolytica* are common. They form a puzzling and unsatisfactory group both to the physician and the pathologist. In some cases the symptoms and presumably the lesions develop at the end of some chronic disease. In others the condition is of long standing continuing for years, although marked by remissions and exacerbations. These are known as chronic ulcerative colitis. Some of the idiopathic cases, however, may run an acute course; in one of my cases the entire course was of five weeks' duration, yet at autopsy the lesions were unbelievably extensive. As the etiology is unknown they may be classed as idiopathic. It has been suggested by some that the chronic cases are a chronic manifestation of bacillary dysentery, by others that they are due to a specific diplococcus (Bargen). It is more probable that the cause still remains to be discovered, possibly a food deficiency complicated by non-specific infection. In diseases of the intestine such as typhoid, tuberculosis and dysentery the infecting agent is all-important. It may well be that this is not the case in ulcerative colitis. Here there seems to be something lacking in the patient or rather the patient's bowel. Under the best hygienic conditions he may recover for a time and remain well, but when he is subjected to strain, overwork, etc., the symptoms and lesions return once more.

**Chronic Ulcerative Colitis.**—The chief symptom is diarrhea, with blood, pus, and mucus in the stools. Secondary anemia and loss of weight are common. The roentgen-rays show a hyperactive colon with loss of the normal haustrations (pipe-stem colon). With the sigmoidoscope ulcers are seen scattered over the reddened mucous membrane of the sigmoid and rectum. The ulcers are covered with mucus and



bleed at the slightest touch, so that it is no wonder that blood in the stools is common.

The ulcers which form the principal lesion are usually confined to the colon and rectum. In fatal cases the entire large bowel may be covered with ulcers which vary from tiny erosions to ulcers several inches in diameter. Sometimes they are arranged along the line of the *Tænia coli*. The ulcers are usually quite superficial, involving only the mucosa, but the muscular coat may also become necrotic, so that occasionally the base may come to be formed by the peritoneum with great danger of perforation. The intervening mucosa is often swollen and edematous so that polypoid masses project from the surface (colitis polyposa). One of these polypi may become malignant. The wall of the bowel may be very friable, so that the sigmoidoscope has to be used with care. The mesenteric lymph nodes are sometimes enlarged and inflamed.

The *microscopic appearance* is that of a chronic bacillary dysentery. At the site of the ulcer the mucosa has disappeared, but the submucosa is much thickened and infiltrated with round cells and leucocytes. The muscular coat is sometimes involved, and the peritoneum over the deep ulcers is thickened. The mucosa between the ulcers is thick, congested, and edematous. *Healing* occurs with very little scarring, so that there is no danger of stricture of the bowel.

**Uremic Enteritis.**—In uremia there may be severe diarrhea, with purulent or bloody stools. The lesions are ulcerative and necrotizing. There are numerous ulcers in the large bowel and the lower part of the small bowel, particularly in the lymphoid tissue. The enteritis is associated in some way with urea retention, for similar lesions can be produced in dogs by the intravenous injection of urea.

### TYPHOID FEVER

Typhoid fever may be regarded as an intestinal disease, for the more obvious lesions are the ulcers of the bowel and it is they which give rise to the dangerous complications, hemorrhage and perforation. But it is really a general infection of the whole body, though the initial lesions are in the bowel, so that it is considered in connection with the Infectious Diseases, p. 156.

### CHOLERA

Cholera is an acute inflammatory condition of the intestine produced by Koch's spirillum and occurring mainly in tropical countries. Infection is due to drinking polluted water. The wise Chinese are the only Orientals who do not suffer from cholera; they use boiled water and cooked food, they drink tea and eat hot rice. Like bacillary dysentery it is an example of a purely local infection, the other organs merely showing the effects of toxemia. Both the large and small intestine are much distended with watery fluid like thin barley soup. As a result of the constant passage of these watery stools (rice-water stools) the patient becomes extremely dehydrated. The entire length of the mucous membrane is intensely congested, being of a deep red color. Hemorrhages are common. Unlike typhoid and dysentery, there is no ulceration.

The epithelium covering the mucosa is shed off so that a raw surface is left, but the mucosa itself is not destroyed, although infiltrated with inflammatory cells. The lymph follicles are swollen and the mesenteric lymph nodes may be necrotic. The spirilla are found in the intestinal contents and in the bile.

The other organs show the effect of acute toxemia (cloudy swelling, focal necrosis). There is acute splenic swelling. A striking feature is the extraordinary degree of rigor mortis, the arms and legs being as stiff as iron rods. Inoculation against the disease is now of great value. In a barracks of 180 men only 4 were uninoculated, and 3 of these were the only ones to get the disease.

### TUBERCULOSIS OF THE INTESTINE

Tuberculosis of the intestine may take two different forms, the ulcerative and the hypertrophic.

**Ulcerative Tuberculosis.**—The infection is usually secondary to pulmonary tuberculosis. In children the intestinal lesion may be the primary one and is caused by drinking tuberculous milk. This is rare in America, but fairly common in England where much more tuberculous milk is consumed. The secondary type of lesion is due to massive infection from sputum which has been swallowed. A few bacilli do not seem to produce a recognizable lesion. For this reason the condition is usually associated with the presence of large cavities. Ulceration of the bowel is the commonest complication of pulmonary tuberculosis, and is found in from 50 to 80 per cent of the cases which come to autopsy; but it is by no means only a terminal occurrence.

The method of infection appears to be as follows: a massive dose of bacilli is swallowed, and the organisms pass into the tubular glands of the intestinal mucosa, where an inflammatory exudate is produced in the depths of the gland. The bacilli are then carried through the epithelial lining by phagocytic cells, and thus reach the submucosa where they give rise to the usual tuberculous lesions. The overlying mucosa may now be cast off with the formation of an ulcer, or it may remain intact so that the bowel may be tuberculous though not an ulcer can be seen. The bacilli may be carried from the submucosal lesion to the mesenteric lymph nodes which drain that segment of the bowel, and there produce caseous lesions. Mesenteric lymph node tuberculosis indicates intestinal tuberculosis but not necessarily intestinal ulceration.

**Symptoms.**—The symptoms are general and local. The general symptoms are those of pulmonary tuberculosis, *i. e.*, loss of weight, asthenia, etc. Every case of pulmonary tuberculosis which does poorly but with no increase in the physical signs should suggest intestinal ulceration. The local symptoms are abdominal pain, diarrhea, and the presence of pus and blood in the stools.

**Lesions.**—The first lesions appear in the ileocecal region, although at autopsy they may be scattered over a wide area. From this site of election the disease spreads up and down. As is usual with tuberculosis, the earliest lesions are in the lymphoid tissue and appear as small gray tubercles in the Peyer's patches and solitary follicles, which becomes yellow from caseation, soften, and break down. (Fig. 242.) The overlying mucosa undergoes necrosis and is cast off, the underlying

caseous tissue is discharged, and an *ulcer* with ragged undermined edges is formed. (Fig. 243.) In the small bowel the ulcer may extend as far as the peritoneum, but in the large bowel it is shallower and seldom penetrates the muscularis. Small tubercles can be seen on the serous coat, or they may be covered up by a plastic exudate. The overlying



FIG. 242.—Tuberculosis of the bowel. There are two shallow tuberculous ulcers.

peritoneum is usually thickened so that perforation is uncommon. The ulcer is supposed to spread transversely across the bowel (girdle ulcer), but quite often it lies in the long axis, especially when it is confined to a Peyer's patch. The *mesenteric lymph nodes* are enlarged and may be caseous. Extension of the inflammation outside the bowel leads to *adhesions*, and these by contracting produce acute *kinks* of the bowel

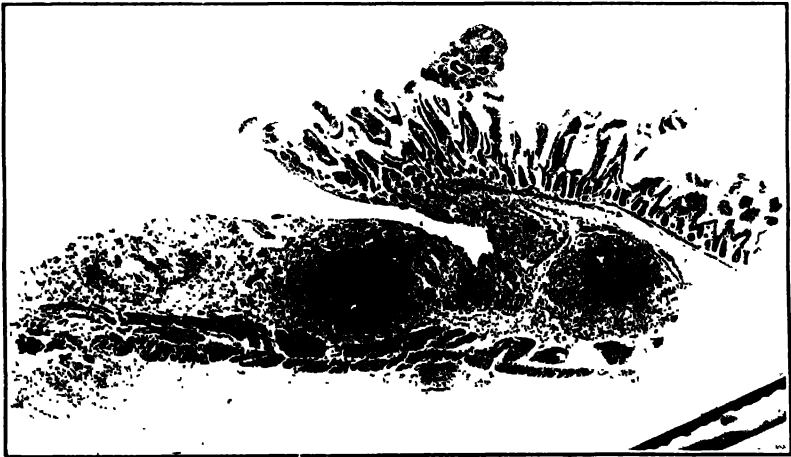


FIG. 243.—Tuberculous ulcer of bowel showing undermined edge and areas of necrosis in the base.  $\times 15$ .

which are a common cause of intestinal obstruction. The *microscopic picture* is one of tuberculous foci with epithelioid cells and lymphocytes, giant cells, and caseation. (Fig. 244.) Endarteritis obliterans is common, and this usually prevents a large hemorrhage from occurring.

*Healing* is common, especially with modern methods of light treatment. The mucosa may be completely restored when the ulcer is shallow, and even deep ulcers become filled with granulation tissue and covered by a simple epithelium. But when destruction of tissue is extensive, cicatrization is correspondingly great, and if the ulcer is of the girdle type stenosis may result. These strictures are often multiple. Serious obstruction is much more likely to be due to kinks of the bowel

produced by adhesions than to cicatricial stenosis, but in the primary lesions seen in children the cicatrices may lead to a marked degree of obstruction.

*Perforation* of a tuberculous ulcer may be complete or incomplete. *Complete* perforation in the general peritoneal cavity occurs in the small intestine where the ulcers are deeper, but it is not common owing to the thickening of the peritoneum. *Incomplete* perforation, which is much commoner, is seen in the large bowel, especially in the right iliac fossa, where it gives rise to a fecal abscess walled off by dense adhesions.



FIG. 244.—Tuberculosis of bowel.  $\times 100$ .

and degenerative lesions of the myenteric plexus of Auerbach. The site of the disease is also related to the diarrhea; lesions of the small bowel are generally associated with constipation, those of the large bowel and especially the descending colon with diarrhea. *Occult blood* in the stools and *pus* in small amount are due to the intestinal ulceration.

**Hypertrophic Tuberculosis.**—The disease, which is rare in comparison with the ulcerative form, commences in the ileocecal region and often remains confined to that part of the bowel, but it may extend up along the ileum and down along the cecum. It is a disease of young adults and is rare over the age of forty years.

The process is formative rather than destructive. There is a great

**The Relation of Symptoms to Lesions.**—The *general symptoms* bear no relation to the lesions. The *pain* is not caused by the ulcers, for these are insensitive. It is due to spasm of the bowel, involvement of the peritoneum, or tuberculous lymphadenitis. The *diarrhea* is related to the hypermotility of the bowel which forms a striking feature of the roentgen-ray picture rather than to the ulceration. The hypermotility seems to depend in turn on inflammatory

formation of granulation tissue chiefly in the submucous but also in the subserous coat. The mucosa is folded and nodular and projects into the lumen causing narrowing, which is sometimes extreme and is easily mistaken for malignant obstruction. The diseased bowel is thick and stiff, and forms a tumor-like mass which is often taken by the surgeon for carcinoma. Enlargement of the regional lymph nodes adds to the difficulty of diagnosis in the operating room. The *microscopic picture* differs from that of the ulcerative form, for though giant cells are numerous in the granulation tissue, definite tubercles are not common and caseation is usually absent. The process is diffuse and hyperplastic, whereas in the ulcerative form it is focal and destructive.

The hyperplastic form is probably a primary infection, perhaps bovine in type, while the ulcerative form is almost always secondary, at least in adults. If there is a fairly high grade of resistance, if there is a small dose of infection, and if the bacteria are of low virulence (bovine), the hyperplastic form may be expected. If the resistance is feeble, the dose large, and the bacteria of high virulence (human), the lesions are likely to be of the ulcerative type (M. J. Stewart). It is more than possible that many of the cases reported may really be examples of sarcoidosis.

**Regional Ileitis.** - In 1932 a non-specific chronic inflammatory condition of the small bowel was described by Crohn and his associates under this name. The site of election is the final 12 or 18 inches of the ileum, ending abruptly at the ileocecal valve (Fig. 245), so that it



FIG. 245.—Regional ileitis.

has been called terminal ileitis, but other segments of the small and even the large intestine may be involved. The affected part is thick, heavy, and reddened. The lumen is narrowed, the intestine above becoming dilated. The mesentery is stiff and greatly thickened, and adhesion of the bowel to neighboring structures (bowel and abdominal wall) is followed by slow perforation and fistula formation. *Microscopically* the picture is usually singularly non-specific, consisting of marked edema of the submucosa and to a lesser degree of the other coats, together with lymphocytic infiltration and a varying amount of ulceration. One of the most remarkable features is the patchiness of

the lesions. In some cases there is a lymphadenoid hyperplasia of the submucosa with the formation of non-caseating giant-cell systems resembling those of Boeck's sarcoid (Hadfield). In the later stages ulceration may obscure and obliterate the primary lesion in the submucosa, but the giant-cell systems may still be found in the regional lymph nodes. The outstanding clinical features are a mass in the right iliac region, diarrhea and fever. The disease may begin with an attack like appendicitis, thus resembling actinomycosis of the bowel. The etiology is obscure, but such lesions might be caused by the lipoid of dead tubercle bacilli.

### ACTINOMYCOSIS OF THE INTESTINE

Actinomycosis of the bowel usually occurs in the cecum or appendix, but occasionally in the pelvic colon. A mass of granulation tissue is formed in the submucosa, followed by ulceration of the mucous membrane. The cecum shows the same great thickening as in the hyperplastic form of tuberculosis, but suppuration occurs and the mass is covered into a nest of abscesses. The disease may spread to the abdominal wall with the formation of a sinus from which pus is discharged containing the characteristic sulphur granules in which the ray fungus is readily demonstrated. The liver may become involved by way of the portal vein, and is eventually riddled with abscesses. Actinomycosis of the cecum is apt to be mistaken clinically for hyperplastic tuberculosis or carcinoma.

**Syphilis.**—Syphilis of the intestine is extremely rare, although gunnatus ulcers have been reported. What used to be frequently diagnosed as syphilis of the rectum causing stricture is now known to be lymphogranuloma venereum.

### APPENDICITIS

In discussing the general features of appendicitis it is convenient to consider the acute form. It must be realized that acute does not necessarily mean severe. Acute inflammation of the appendix slight in degree is very much commoner than the severe variety. A distinction has been drawn between acute appendicitis, *i. e.*, primary inflammation of the wall due to infection from the blood or intestine, and acute appendicular obstruction (Wilkie). As will be seen presently, this distinction is probably one rather of degree than of kind.

**Etiology.**—The etiological factors are exciting and predisposing. The two great *exciting* factors are obstruction and infection. It is becoming more and more apparent that the former is the dominant factor. Wangenstein and Bowers found that complete obstruction of the infected cecal appendage in the dog always results in inflammation, whereas if there is infection without obstruction or obstruction without infection no inflammation develops. Pressure-distention is an exciting factor of first importance; increased pressure within the lumen for six to twelve hours causes inflammatory changes in the walls. There is a sphincter-like mechanism at the base of the appendix which makes it

a potential closed loop, and is probably responsible for the formation of concretions. Wangenstein and Bowers found that when a needle was passed through the tip of the uninflamed human appendix at operation and attached to a column of water, not a drop escaped into the cecum with a pressure of 40 cm. of water. This suggests that a sphincter-like mechanism exists at the proximal end of the appendix which may be stimulated to contract by increase of pressure within the lumen as well as through the extrinsic nerves. The symptoms of appendicitis can be produced by tying the base of the appendix and slowly distending the lumen by injecting saline solution. Obstruction, then, may be caused not only by the easily recognized concretion (Fig. 246), but by contraction of the sphincter, as well as by swelling of the abundant lymphoid tissue in the wall, previous fibrosis of the proximal end, acute kinking by a band of old adhesions or by a congenital fold. Wangenstein and Bowers found obstruction in 72 per cent of cases of acute suppurative appendicitis and in 100 per cent of gangrenous appendicitis (80 per cent concretions). In most cases, then, obstruction seems to be a much more important initial factor than infection. The acute attack has been likened to a knock at the door saying, "Let me out." As the result of obstruction the lumen becomes distended, the intraluminal pressure increased and the venous return interfered with, so that the vessels rupture, hemorrhage occurs, the wall is poorly oxygenated and invaded by bacteria, the swelling increases, and perforation is the end-result. There is no doubt that a blow on the abdominal wall may occasionally precipitate an acute attack of appendicitis. As might be expected, mild cases are much more likely to have had multiple attacks, because the obstruction is slight and is overcome spontaneously, so that the patient can go on to another attack. The severe (gangrenous) cases have few previous attacks, because the obstruction can only be overcome by perforation of the appendix; it is natural that fecaliths causing complete obstruction should be common in these cases.

The infecting organisms appear to invade the mucosa from the lumen. They are probably the normal inhabitants of the appendix. Streptococci and *B. coli* are most commonly found, often in combination. The streptococcus is probably the chief infective agent, for



FIG. 246.—The obstructive element in acute appendicitis. Fibrous stenosis of proximal end, dilatation and thinning of distal half, and occlusion of lumen by a fecalith.

the inflammation tends to spread throughout the organ in the same manner as streptococcal infections elsewhere. It is probable that in exceptional cases infection may be by the blood stream, as when acute appendicitis occurs in the course of acute tonsillitis or septic sore throat.

The *predisposing causes* are indefinite. The disease is commonest in the second and third decades; it is rare in infancy and old age. Previous damage to the appendix with fibrosis predisposes to future attacks. The disease is common in highly civilized countries and urban communities, but rare in remote rural districts and among primitive peoples. During the nine years that McCarrison practised among the hill tribes of the Himalayas he never saw a case of appendicitis. Natives who live on a diet abundant in cellulose are immune from the disease, but when they adopt the diet of civilization they lose that immunity. These and many other similar facts suggest that habits of life, and in particular modes of diet such as meat-eating, are of importance in predisposing toward appendicitis.

It is very difficult to hit on a classification of appendicitis which will be satisfying both to the pathologist and the clinician. The pathologist is primarily interested in reporting on appendices which have been removed by the surgeon. These may be divided into the following groups: acute appendicitis, healing appendicitis, fibrosed appendix, and normal appendix. The last need not be considered further.

*Acute Appendicitis.*—Acute inflammation of the appendix may take a variety of forms. It may be mild with correspondingly mild symptoms, a condition to which the clinician is fond of applying the quite unjustifiable term *catarrhal appendicitis*. A patient may suffer from a succession of mild attacks, and it is to these recurring attacks that the clinician applies his favorite name of *chronic appendicitis*. In other cases the inflammation is severe and purulent. These may be called *acute suppurative appendicitis*. Gangrene may be present, particularly when there is an element of obstruction (Wilkie); these are cases of *gangrenous appendicitis*.

In *acute suppurative appendicitis* the infection seems to begin at the bottom of one of the crypts, where a small focus of suppuration is formed in the mucosa. (Fig. 247.) The organisms apparently do not readily spread through the mucosa, because that coat may be apparently normal apart from one or two points of abscess formation although the rest of the appendix is acutely inflamed. The spread takes place in the loose submucosa, and from there through the muscularis along the line of the penetrating vessels to the subserous coat, where it again becomes diffuse. In looking for evidence of inflammation, therefore, attention should be directed to the submucous and subserous layers. By the time the appendix is removed the muscularis and peritoneal surface are usually also inflamed.

The appendix is swollen and elongated, bright red in color, with dilated subperitoneal vessels and a fibrinous or purulent exudate (some-



times very slight) on the surface. There may be yellow spots on the surface indicating the beginning of an abscess. The tip is usually swollen, and the whole process is likely to be more marked in the distal than the proximal part. When the appendix is opened the mucosa is seen to be swollen and very congested. The surface is granular or warty. Superficial erosions are common, but there may also be ulcers which penetrate to the submucous coat and sometimes to the peritoneum. The lumen may be narrowed owing to swelling of the mucosa, but if that layer is destroyed it may be dilated and filled with pus.



FIG. 247.—Acute appendicitis. Small mucosal abscess rupturing into the lumen.  $\times 26$ .

*Microscopically* all the coats are congested, edematous, and infiltrated with polymorphonuclear leucocytes, but the mucous membrane may show little or no infiltration. The normal cellularity of this membrane makes it difficult to be certain of slight changes in the number and kind of cells. Eosinophils may be very abundant, especially when the acuteness of the inflammation is passing off. Necrosis of the mucosa is common, and masses of dead membrane may be cast off, thus forming ulcers especially at the points where the lymph follicles approach the surface. There may be hemorrhages in the mucosa which often leave a permanent pigmentation. The mesentery of the appendix shares in the inflammation, being thickened, edematous, and infiltrated with polymorphonuclear leucocytes. Thrombosis of the vessels may occasionally give rise to abscess formation in the liver (portal pyemia).

*Gangrenous appendicitis* is one variety of acute suppurative appendicitis. There is death and putrefaction of the tissues of the appendix due to interference with the blood supply. The gangrene is often local, appearing as a green or black patch at the distal end, often at the tip. (Plate XII.) A concretion which is sometimes quite hard is often found at the site of gangrene, and has no doubt played an etiological part by pressing on the stretched and inflamed wall. Gangrenous appendicitis is very different from simple acute appendicitis, because it is invariably fatal unless the appendix is promptly removed owing to rupture of the wall and flooding of the peritoneal cavity with highly infective material. Simple acute appendicitis, on the other hand, has a strong tendency to spontaneous recovery.

*Perforation* may occur at any stage of acute appendicitis, but is commonly associated with gangrene. The ulceration of the mucosa already described may penetrate the muscular and serous coats causing perforation. A fecal concretion is often present at the site of the perforation, and evidently plays a part in its production. It may escape into the abdominal cavity. If the perforation occurs into the open peritoneal cavity *general peritonitis* will at once be caused by the flooding of the membrane with septic material. Often, however, the inflamed part of the appendix is surrounded by a layer of omentum which becomes adherent to it before perforation has time to occur. In this case a *local appendicular abscess* will be formed, and there may be no infection of the general peritoneal cavity. The abscess may involve the anterior abdominal wall, and when it is opened a *fecal fistula* may result, through which fecal matter is discharged from the appendix on to the abdominal wall.

*Mild attacks of acute inflammation* are very common. From the pathological standpoint acuteness must not be confused with severity. In these cases the appearance of the appendix is very different. It is slightly swollen, the surface vessels are dilated, but there is no peritoneal exudate. The submucous coat shows a moderate infiltration with inflammatory cells, and the subserous coat to a lesser degree. Many of these cells may be lymphocytes instead of polymorphonuclears. It sometimes happens that very little inflammation may be found to account for the rather severe symptoms. In these cases, particularly in young people, there may be great swelling of the lymph follicles in the mucosa which are not only much larger but appear to be more numerous than normal. It is possible that this lymphoid hyperplasia may cause stretching of the serous coat with pain as a result. Healing is the rule, with fibrosis and thickening of the submucosa. There may be repeated attacks followed each time by further change in the wall of the appendix, so that finally the appendix may be converted into a solid cord of fibrous tissue with no lumen and no differentiation between the different coats. These cases are likely to be diagnosed by the clinician either as catarrhal appendicitis or chronic appendicitis. The progressive fibrosis of the wall of the appendix renders it liable to an attack of acute appendicular obstruction.

## PLATE XII



FIG 1



FIG. 2

Fig. 1.—Carcinoid Tumor of Appendix Showing the Characteristic Yellow Ring.

Fig. 2. Gangrenous Appendicitis. The Distal Third is Gangrenous, and is About to Perforate at the Lower Border.

*(Boyd's Surgical Pathology, courtesy of W. B. Saunders Company.)*



*Healing Appendicitis.*—The appendix is often removed a few weeks after an acute attack has passed off. It may be slightly swollen or of normal thickness. The polymorphonuclears in the submucous and subserous coats are replaced by chronic inflammatory cells, chiefly lymphocytes but sometimes with such large numbers of eosinophils that the affected part looks red under the low power. The lymphocytes in the subserous coat may have a perivascular distribution, and the general picture may strongly suggest chronic inflammation. Very many appendices which are diagnosed by the laboratory as chronic appendicitis are really examples of healing appendicitis. The inflammation is transient, not chronic.



FIG. 248.—Fibrosis of appendix; inset shows normal thickness of coats. (Boyd's Surgical Pathology.)

*Fibrosis of the Appendix.*—The term *chronic appendicitis* is applied by the surgeon to a thickened and fibrosed appendix which he may remove at operation. This is likely to be either the healing stage of acute appendicitis or fibrosis of the appendix resulting from recurring mild acute attacks. It is doubtful if there is such an entity as chronic appendicitis in the sense of a slowly progressive inflammation without acute exacerbations. Although symptoms such as dyspepsia and discomfort in the right iliac fossa may be relieved temporarily by removal of the appendix, a careful follow-up history will show that these symptoms will eventually recur.

The fibrosed appendix is thickened and rigid. The fibrosis is most marked in the submucous and serous coats (Fig. 248), but if the mucosa has been destroyed, the lumen may be obliterated. Dilated lymphatics in the subserosa may contain collections of lymphocytes, but these are also seen occasionally in normal appendices. In old age the appendix may be pale, withered and shrunken, with obliteration of the lumen, and fusion of the coats into a fibrous mass. This may be regarded as a non-inflammatory atrophy.

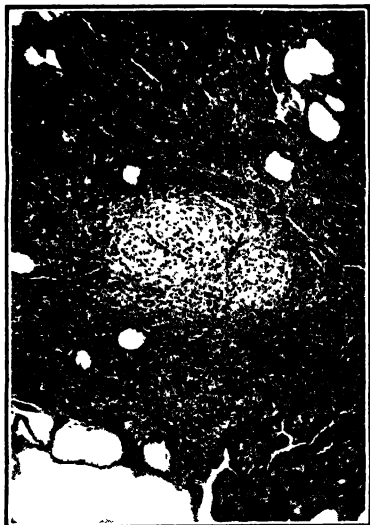


FIG. 249.—Neurinoma in fibrosed appendix. (Masson's trichrome stain.)  $\times 50$ .

Masson has shown that the normal appendix contains a large amount of non-medullated nerve fibers, and that this amount may be greatly increased as the result of inflammation. In the infant plain muscle bundles accompanied by the nerves of Meissner's plexus can be seen to pass inward from the circular muscle coat and outward from the muscularis mucosæ to anastomose in the submucosa and form a "neuromuscular complex." In the adult the presence of lymph follicles makes this arrangement less easily detected. Sometimes the submucosa shows a remarkable hypertrophy of the neuromuscular complex. The mucosa may also be thickened, and may contain numbers of small circumscribed neuromas (neurinomas). (Fig. 249.) It remains to be seen whether hyperplasia of this nerve

tissue may be responsible for symptoms in the right iliac fossa, and whether the term "neurogenic appendicitis" is justifiable.

*Mucocele of the appendix* is a condition in which stenosis of the proximal part results in distention of the distal part with clear mucinous fluid to form a cyst. In rare cases the mucocele may be the starting point of *pseudomyxoma peritonei*, rupture of the cyst being followed by implantation of epithelial cells on the peritoneal surface, and the formation of large mucoid masses like frog's spawn.

In *Graves' disease* there is sometimes tremendous lymphoid hyperplasia of the appendix; the proliferating lymphocytes may wipe out the mucosa, infiltrate the muscular wall, and obliterate the lumen.

In *measles* during the prodromal stage giant cells are found in the germ centers and neighboring lymphatic tissue of the appendix, and in the regional lymph nodes. The giant cells may be 100 microns in diameter, and contain from 50 to 100 nuclei.

**The Relation of Symptoms to Lesions.**—Apart from fever and leucocytosis which are due to the infection, the chief symptoms are nausea, vomiting, and local pain and tenderness. In acute appendicitis the hyperemia and inflammatory exudate cause distention of the organ with stretching of the sym-

pathetic plexus which lies in the outer part of the wall. The stimuli pass to the semilunar ganglia and give rise to nausea, vomiting, and general abdominal pain. The inflammation soon reaches the serous coat, and the inflammation of the *parietal* peritoneum is the cause of the local pain and rigidity. The local symptoms are more severe and more sudden in onset when acute obstruction is a marked feature, because the distention of the appendix is much greater. In the most severe and fulminating cases the local symptoms may be slight except at the very beginning, because the rapidly developing gangrene soon destroys the sympathetic nerve endings.

The problem of so-called chronic appendicitis is much more complex and cannot be discussed here. On purely pathological grounds it does not seem reasonable to suppose that the multitudinous symptoms of "chronic appendicitis" (chronic dyspepsia, vague abdominal pain and tenderness over the appendix are the classical ones) can be caused by fibrotic changes in the appendix. But it is possible that at least in some cases Masson's neuromuscular hyperplasia may represent the anatomical substratum of the symptoms.

## TUMORS OF THE INTESTINES

**Carcinoma.**—Carcinoma is a common tumor of the intestine. The usual sites of cancer are the rectum, cecum, and pelvic colon. Cancer of the small intestine is very rare. Over 60 per cent of cancers of the bowel occur in the rectum. Precancerous lesions which may be followed later by carcinoma are papilloma, adenoma, and the papillary formation occurring in chronic ulcerative colitis. By far the greatest danger is familial multiple papillomata. Precancerous lesions in the rectum are of special significance.

The site of cancer of the large bowel affects its behavior and characteristics to a marked degree. Thus cancer of the colon is more common in women, cancer of the rectum more common in men. The average duration of life without treatment is twice as long in cancer of the rectum as in cancer of the colon. Intestinal obstruction is much commoner in cancer of the descending colon and rectum than in cancer of the cecum, due to the fluid contents of the latter.

The tumor may (1) grow into the lumen of the bowel in the form of a large fungating cauliflower-like mass which soon becomes ulcerated, or (2) it may infiltrate the wall and surround the bowel as an annular growth which may cause an extreme degree of stenosis. (Fig. 250.) The bowel above the stenosis is dilated and hypertrophied, that below the stenosis is collapsed. Hard fecal masses may be formed on the proximal side of the stricture and these may give rise to superficial erosions of the mucosa (stercoral ulcers). The fibrous stroma of the second form of tumor contracts, and from the outside it may look as if a tight string had been tied around the bowel (purse-string type). In this form ulceration occurs late. Mucoïd degeneration may occur in the massive variety, and the large bowel is one of the common sites of the so-called colloid carcinoma.

The *microscopic appearance* is that of adenocarcinoma. The fungating type is more likely to be well differentiated than the infiltrating form, which may develop a dense stroma. The prognosis depends largely on the degree of differentiation, *i. e.* the grade to which the

tumor belongs. In cancer of the rectum Grades 1 and 2 are best treated by excision, Grades 3 and 4 by radiation.

*Spread.*—This is comparatively slow, especially in cancer of the rectum, so that the prognosis is correspondingly good. In a case of cancer of the rectum the tumor protruded from the anus, and was partially removed from time to time for seventeen years after the condition had been called inoperable, yet at autopsy there was no evidence of metastases (Wells). Growth takes place easily towards the lumen and also in the long axis of the bowel; infiltration of the muscular coat is much slower.



FIG. 250.—Carcinoma of the large bowel. There is almost complete obstruction, and above the obstruction the bowel is greatly dilated.

After penetration of the muscular coat there is again spread in the long axis in the subserous tissue; the lymphatics may be distended with cancer cells and appear as opaque white beaded lines which may be mistaken at operation for tubercles. Involvement of the mesenteric and retroperitoneal lymph nodes occurs late, and so do metastases to the liver by the portal vein. I have performed an autopsy on a patient who had had cancer of the rectum over a year for which she refused operation and who finally died of pneumonia, yet neither the lymph nodes nor the liver were involved in the slightest degree. The cancer cells may penetrate the serous coat and give rise

to implantation growths on the peritoneum and the surface of the pelvic organs.

**The Relation of Symptoms to Lesions.**—The early symptoms are unfortunately vague, *e. g.*, persistent constipation with occasional attacks of colicky pain which may finish as acute obstruction. A change in the habitual action of the bowels is always a danger signal. The classical text-book symptoms are late symptoms and usually indicate that the tumor is inoperable. The stools may be ribbon-like, due to malignant stricture in the infiltrating type. In the fungating type there is hemorrhage from the friable surface, and when ulceration and infection occur there are foul stools and alternating constipation and diarrhea. Blood in the stool is an early sign of cancer of the rectum, but a late sign of cancer of the sigmoid. Cancer of the cecum is often associated with severe anemia, sometimes pernicious in type, an association which it is difficult to explain.

**Papilloma.**—Multiple papillomata or adenomatous polypi may occur in any part of the intestinal canal, but are most common in the large



bowel, especially in the rectum. They may be very numerous, and the entire large bowel may be studded with polypi, a condition known as multiple polyposis of the intestine. The condition is often hereditary (familial). Papillomas and adenomas of the bowel must be regarded as precancerous lesions, especially in the rectum. (Fig. 251.) The incidence of carcinoma in a single adenomatous polyp is about 5 per cent. The structure of the papilloma is glandular, and the malignant change is into adenocarcinoma, the line of change often being dramatically sharp. (Fig. 252.) Usually only one papilloma becomes malignant, but more than one may show the change. In papillomatosis there may be as many as one or two thousand, so that the chance of escaping carcinoma in such a case is infinitesimal. The incidence of carcinoma is directly proportional to the number of papillomata.



FIG. 251.—Malignant papilloma of rectum.

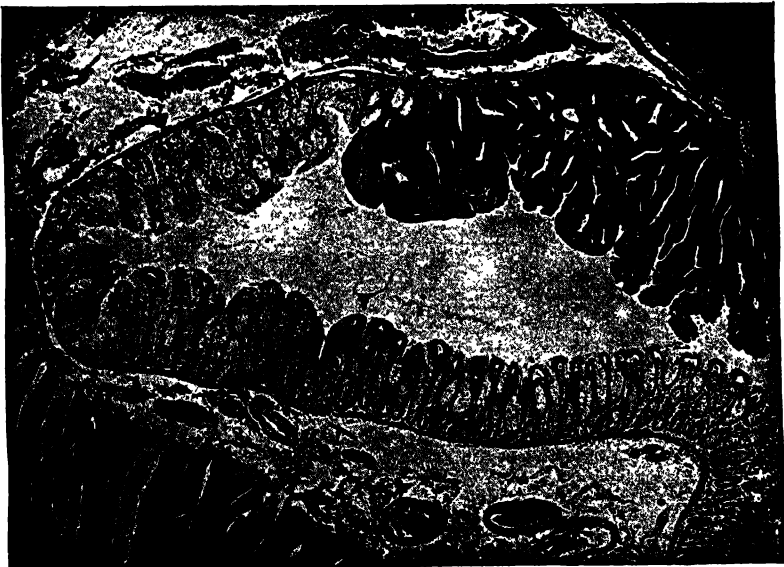


FIG. 252.—Transition from adenoma to carcinoma.  $\times 20$ . (Boyd's Surgical Pathology.)

**Carcinoid Tumor.**—This is not an uncommon tumor of the appendix. It may occur in the small bowel, particularly at the lower end of the ileum, where it is rare. It should be regarded as a malignant tumor usually of very low grade. In the appendix it may infiltrate all the coats, but very seldom spreads to the lymph nodes, and never kills the patient. The tumors in the intestine are more dangerous. They may be multiple, tend to produce obstruction, metastasize to the regional lymph nodes in 25 per cent of the cases, and occasionally to the liver. In the appendix the tumor usually gives rise to no symptoms, unless it causes obstruction at the proximal end, and is usually discovered by accident after the appendix has been removed. The appendix itself is rarely normal, being thickened and fibrosed.



FIG. 253.—Carcinoid of appendix. There are masses of tumor cells in the mucosa and submucosa.  $\times 150$ .

The *gross appearance* is very characteristic. Usually at the tip of the appendix a firm nodule can be felt, which on cross-section appears as a yellow ring encircling the appendix and situated in the thickened submucous coat. (Plate XII.) *Microscopically* the tumor consists of masses of spheroidal or polyhedral cells with granular or finely vacuolated cytoplasm. These cells are rich in lipid, and it is to this that the yellow color of the tumor is due. The tumor cells are usually confined to the mucous and submucous coats, but they may reach the serous coat. (Fig. 253.)

It appears from the work of Pierre Masson that these tumors are *chromaffinomas* or tumors of the endocrine system, arising from the Kultschitsky cells of the intestinal mucosa which are found between the columnar cells of the crypts of Lieberkühn and belong to the chromaffin system. Both the Kultschitsky cells and the tumor cells are stained intensely by silver impregnation, so that the tumor is also called an *argentaftinoma*. These chromaffin or argentaftin tumors are occasionally found in the small intestine.

There may be a relationship between carcinoid tumors and the argentaftin-cell neuromas which Masson had previously described as occurring in obliterated appendices. These neuromas arise from the non-medullated nerve fibers in the deeper part of the mucosa. According to Masson the argentaftin cells actually migrate into the nerve fibers, which then grow and form a neuroma. If the isolated argentaftin cells in the neuroma proliferate, a car-

cinoid tumor is produced. This part of the work, which depends on the use of Masson's trichrome method of staining, still awaits confirmation.

*Carcinoma of the appendix* is very much rarer than carcinoid tumors. It is a columnar-cell carcinoma, frequently adenocarcinomatous in type, and often shows mucoid degeneration.

All other primary tumors of the bowel are rare. *Sarcoma* is more usual in the small than the large intestine. *Fibroma*, *myoma* and *lipoma* often take a polypoid form and may act as the starting point of an intussusception. *Angiomas*, sometimes multiple, have been described. *Lymphosarcoma* is not uncommon in the bowel, but as it is merely part of a general lymphoid tissue neoplasia it will not be considered here.

### INTESTINAL DIVERTICULA

Diverticula of the intestine usually occur in the duodenum and the lower part of the colon, but they may be met with in any part of the intestinal canal. Duodenal diverticula have already been described. The usual age period is in middle and late life. They are rare before the age of thirty years. In the small intestine they lie in the concavity of the bowel along the line of the mesenteric attachment, as the entering vessels serve to weaken the muscular wall. In the colon they are situated on the convexity, usually in two rows between the *tænia coli*. The commonest site is the sigmoid, but they usually stop abruptly at the commencement of the rectum, because here the *tænia coli* separate out into a broad muscular sheet. Occasionally diverticula occur in the rectum.

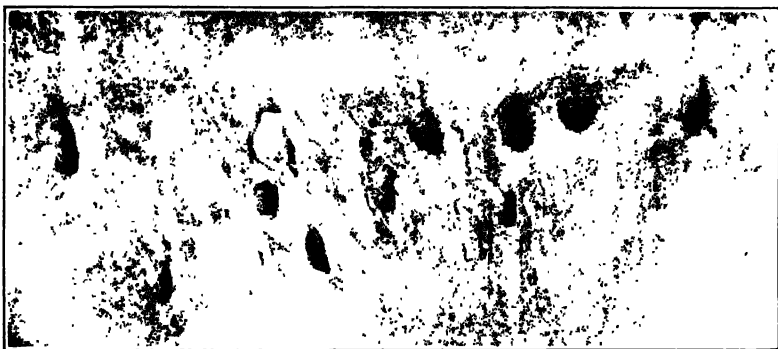


FIG. 254.—Intestinal diverticulosis, showing the openings of the diverticula on the mucosal surface.

The diverticulum is a protrusion or herniation of the mucosa and submucosa through the muscular coat at some point of weakness. Diverticula may be present in great numbers, a condition of *diverticulosis*. The usual size is that of a large pea. The opening into the lumen of the bowel may be very small or wide and gaping. (Fig. 254.) In the small intestine the contents are fluid, but in the colon they are fecal and sometimes in the form of concretions.

The *cause* of the condition is uncertain. There is probably a com-

bination of weakness of the wall and increased pressure from within. The weakness seems to be due to the loss of tone and elasticity of muscle which is characteristic of the degenerative period of life.

**Diverticulitis.**—The condition of diverticulosis is unattended by symptoms, and is often discovered accidentally by the radiologist. But if inflammation occurs in the diverticula, symptoms will be produced. This is very rare in the small intestine where the contents are fluid and readily pass out of the diverticula, but is fairly common in the colon. Fraser remarks that “in the Century and Oxford dictionaries a diverticulum is described as a ‘way-side shelter or lodging,’ with, from the context, the underlying meaning that they are houses of ill repute where trouble is apt to brew. In the large intestine they live up to their bad reputation, and as a temporary lodging for bowel contents can give rise to endless trouble.” *Acute inflammation* often associated with the presence of a hard concretion in the diverticulum is similar to appendicitis, except that the symptoms are usually on the left side. Perforation may occur, with local abscess formation or general peritonitis.



FIG. 255.—Multiple diverticula of bowel with peridiverticular fibrosis.

*Chronic inflammation* is much commoner, and is accompanied by a *peridiverticulitis*. Toxins apparently leak through the mucosa and set up a chronic extramucosal inflammation, as a result of which a large amount of chronic inflammatory tissue is formed on the outside of the bowel. (Fig. 255.) This consists of granulation tissue which becomes converted into dense fibrous tissue. A large mass is formed which may constrict the bowel and cause stenosis, so that it is readily mistaken for carcinoma even when the abdomen is opened. The diverticula may be completely covered up by the inflammatory mass. When the excised bowel is opened it may be impossible to detect the inner openings of the diverticula, as they may be hidden by the swollen mucosa. If thin slices are cut tangential to the outer surface of the mass the

blind ends of the diverticula are exposed, and a probe can readily be passed through into the lumen of the bowel. On examining the gross specimen it may be difficult to decide if the condition is diverticulitis or carcinoma. A point of value is that in the former the mucosa is practically never ulcerated, while in cancer ulceration is almost always present.

**Meckel's Diverticulum.**—In about 3 per cent of cases the vitelline duct passing from the intestine to the umbilicus fails to become obliterated. As a rule only the proximal part remains open and forms a pouch-like projection from the lower part of the ileum, usually within 2 feet of the ileocecal junction. This is known as Meckel's diverticulum. It may be a mere dimple, or may constitute a fistula which opens on the umbilicus. The proximal part may remain open and be continued to the umbilicus as a fibrous cord. A loop of bowel may be forced around this cord and becomes strangulated. Sometimes the diverticulum becomes acutely inflamed, with symptoms identical with those of appendicitis. In a certain proportion of cases (12 to 44 per cent according to different authors) islands of gastric mucosa are found in the diverticulum. These produce gastric juice, as a result of which peptic ulcer may occur. This may cause severe hemorrhage from the bowel (especially in male children) or perforation. Occasionally the diverticulum may contain pancreatic tissue.

**Enterogenous Cysts.**—These are derived from diverticula of the intestine in which the communication with the bowel has been pinched off. Intestinal structures, both epithelial and muscular, can often be demonstrated in the wall of the cyst.

### HERNIA

A hernia is a protrusion of a viscus outside the cavity in which it is contained. The usual hernia is abdominal (although we speak of cerebral and other hernias), a loop of bowel, sometimes a piece of omentum, being protruded into a pouch of peritoneum which projects outward. This is an *external hernia*, and the common types are inguinal, femoral and umbilical, depending on the site of the peritoneal pouch. An *inguinal* hernia passes down the inguinal canal into the scrotum. A *femoral* hernia passes along the femoral vessels under Poupart's ligament and forms a soft swelling in the groin; it usually occurs in the female. An *umbilical* hernia appears at the umbilicus. A hernia may occur at the site of an abdominal wound owing to the scar giving way. This is a form of *ventral* hernia. The rare forms need not be mentioned. The *causes* are probably twofold: (1) local weakness, usually congenital; (2) increased pressure due to sudden muscular effort, straining at stool, etc.

In an *internal hernia* the protrusion occurs into one of the intra-abdominal pouches of the peritoneum, of which the principal are the paraduodenal pouch on the left side of the second part of the duodenum, the pouch behind the superior mesenteric artery, and the fossæ in the neighborhood of the ileocecal junction. In rare cases there may be a hernia into the foramen of Winslow and other unusual sites.

*Strangulation* of the hernia is due to an increase of pressure in the hernial sac. A fresh piece of bowel may be forced through the opening, or there may merely be an accumulation of gas and feces. The loop of bowel is forced against the sharp edge of the opening so that the venous return is interfered with. This causes further swelling of the loop, more interference with the circulation and finally complete stasis. Necrosis and gangrene rapidly develop, the wall is invaded by bacteria, and general peritonitis is the result. The clinical and pathological picture is now one of acute intestinal obstruction.

### INTUSSUSCEPTION

This is the invagination of one segment of the intestine inside another. The common site is the ileocecal junction. There is usually an exciting cause

in the shape of a focus of local irritation, an adherent tuberculous or malignant gland, or the presence of a polypoid tumor (adenoma, oma, myoma). As a lip result of the irritation irregular peristaltic contractions are set up, and these force the upper segment of bowel into the one below which forms a sheath. The invaginated part is forced along the bowel by peristaltic contractions and may traverse the whole length of the colon, forming a curved thick sausage-shaped mass. The contraction of the sheath prevents the escape of blood from the enclosed part, so that there is great swelling and congestion; there is hemorrhage into the bowel, and discharge of blood from the rectum is the most characteristic symptom. At first the intussusception can readily be undone by traction, but the two layers become inflamed and adhere together at the point of entry. The increasing contraction and pressure are apt to cause necrosis and gangrene of the bowel with symptoms of acute strangulation. The condition usually occurs in boys under the age of one year. It is uncommon in the adult.

Multiple *agonal intussusceptions* are often seen in the small intestine of children at autopsy. They are probably caused by irregular spasmodic contractions at the time of death. There is no inflammation nor adhesions, so that the intussusception is readily undone by traction.

### VOLVULUS

Volvulus is torsion of an organ. It is commonest in an ovarian cyst with pedicle and in the pelvic colon, but may occur elsewhere in the intestine, in the gall-bladder, spleen, testicle, and uterus with fibroids. The cause is obscure. There is probably some predisposing cause (congenital defect of attachment, etc.), and the actual twisting may be due to irregular spasmodic contraction. The vessels, first the veins and then the arteries, are occluded by the twisting of the mesentery, so that first there is intense congestion of the organ and then gangrene. (Plate XIII.) In the case of the bowel there is acute intestinal obstruction.

**Adhesions.**—Peritoneal adhesions are a common result of abdominal inflammation and may cause intestinal obstruction. The adhesion stretches as a fibrous band from the wall of the bowel to some fixed point, and as it contracts it causes kinking and obstruction.

### INTESTINAL OBSTRUCTION

Obstruction of the intestine or ileus may be caused in two very different ways. It may be organic or paralytic. *Organic obstruction* may be caused by carcinoma, adhesions and cicatrices, strangulated hernia, or volvulus. *Paralytic obstruction*, usually called *paralytic ileus* because the common site is the ileum, is due to inflammation of a segment of the bowel as a result of which peristaltic movements cannot pass from the segment above to the segment below, the bowels are unable to move, and the practical result is obstruction. A common cause is the pelvic peritonitis of acute appendicitis, in which a loop of ileum hangs down into a pool of pus in the pelvis and becomes completely paralyzed. Intestinal obstruction may be acute or chronic. In the acute form the blood supply to the bowel is cut off so that gangrene quickly develops; in the chronic form it is not interfered with. This difference is fundamental. The two varieties are so different that they must be considered separately.

**Acute Obstruction.**—Sudden obstruction may be caused by strangulation of a loop of bowel by a fibrous band or adhesion (strangulated

PLATE XIII



Acute Intestinal Obstruction Due to Volvulus

Body opened at autopsy showing gangrenous distended coils of small intestine.





hernia), twisting (volvulus), intussusception or infarction (mesenteric thrombosis or embolism). The last-named belongs to the paralytic group. Chronic obstruction due to carcinoma may suddenly become acute. The bowel below the obstruction empties and remains pale and contracted. The part above the obstruction is greatly dilated with fluid and gas and intensely congested so that it becomes deep purple in color as the veins are obstructed before the arteries. The mucous membrane undergoes necrosis, numerous small ulcers are formed, and bacteria pass through the wall of the bowel and cause general peritonitis. As the blood supply is cut off and bacterial invasion is severe, gangrene quickly develops.

The cause of the fatal toxic symptoms, most marked in high obstruction, has long been a subject of controversy. Absorption of highly toxic split-protein products from the obstructed loop may play some part (Whipple). Loss of chlorides due to the continuous vomiting have been considered of such importance that sodium chloride has been administered as a form of treatment (Haden and Orr), but without any significant impression on the high mortality. It appears probable that the most important factor is distention of the bowel, and that shock plays a leading part in severe and fatal cases. Acute experimental distention of the bowel without obstruction will produce the same symptoms as those of obstruction but without vomiting or change in the blood chlorides (Taylor). The distention is due partly to gas, partly to fluid. The gaseous distention is caused by air which has been swallowed and cannot be passed. Distention of the bowel wall is a powerful stimulant to secretion, so that great quantities of fluid are poured out. Normally from 5 to 7 liters of fluid a day enter the upper part of the small intestine to be absorbed from the lower part. In high obstruction all of this fluid is completely lost to the body, and this loss is responsible for the picture of shock, the basis of which is a marked difference between the volume of blood and the volume capacity of the vascular system. Moon points out that the post-mortem picture of acute obstruction is similar in many respects to that of shock. There is marked distention and engorgement of the capillaries in the viscera, edema and ecchymoses in the lungs and gastrointestinal mucosa, and effusions into serous cavities. Decompression of the distended bowel by means of the Miller-Abbott tube is the most valuable single method of treatment and has entirely changed the prognosis. In addition to the low blood chlorides there is a great rise in the blood urea due probably to increased tissue destruction. Large quantities of indican are excreted in the urine.

One of the most serious features of acute intestinal obstruction is loss of protein from the body. In simple obstruction without strangulation the loss is confined to plasma, so that hemoconcentration is a marked feature. When strangulation is present there is an added loss of red blood cells owing to damage to the vessels, so that the physiological disturbance is similar to that produced by massive hemorrhage.

In acute obstruction a highly toxic fluid collects in the peritoneal cavity; when this fluid is injected into an animal it produces a clinical picture similar to that of acute obstruction. This serves to explain why a patient with a strangulated hernia does not present the same constitutional disturbances as does a patient with an intraperitoneal obstruction, for there is no marked absorption from the sac. Nor does absorption occur from a markedly distended isolated loop of bowel, as can be shown by the experimental introduction of a lethal dose of strychnine into such a loop without ill effect to the animal. When, however, the loop is suddenly decompressed the animal quickly dies of strychnine poisoning.

As the distention increases, the pressure within the lumen closes the veins, the arterial blood continues to be pumped into the bowel wall, and hemorrhage occurs from the capillaries and venules. The progressive anoxia results in necrosis, gangrene, and finally rupture. These changes are greatly aggravated by the presence of feces, which may act as a secretory stimulant. In experimental obstruction if the obstructed loop is first washed out it does not become gangrenous. Even before gangrene has occurred the permeability of the distended bowel to bacteria is greatly increased, so that peritonitis is an inevitable result. Death is not due to the peritonitis but to the obstruction.

In connection with the toxemia of acute intestinal obstruction mention may be made of the experimental *autolytic peritonitis* produced by autolysis of liver tissue in the peritoneal cavity. It is a remarkable fact that when a dog's liver is removed, the animal survives longer if the whole liver is excised than if part of it is left (Mann). When one lobe of the liver is ligated, the animal dies in less than twenty-four hours, and the ligated lobe is spongy, full of gas, and contains great numbers of Gram-positive anaerobic bacilli. If a piece of liver is excised and dropped into the abdominal cavity of the same or another animal, the same thing happens, the animal dying of respiratory paralysis in less than twenty-four hours. The peritoneal cavity contains from 100 to 300 cc. of fluid exudate (peritonitis), and both the transplanted liver and the animal's own liver are swarming with anaerobes and filled with gas. The condition is called autolytic peritonitis because autolysis of the transplanted liver or the ligated lobe appears to cause the formation of toxic substances which increase the permeability of the bowel to *Bacillus welchii*. It is these organisms which invade the liver and are responsible for the gas formation. The same result is obtained when the piece of liver is autoclaved before being transplanted, so it is evident that the bacilli are not contained in the transplant. This work illustrates the importance of the autolytic decomposition of tissue in the peritoneal cavity.

**Chronic Obstruction.**—The obstruction is slow and there is no interference with the blood supply. The usual causes are carcinoma of the bowel, especially the infiltrating variety, cicatricial contraction or adhesions, and pressure from without. Above the stricture the bowel is dilated and hypertrophied, while below it is collapsed. Hypertrophy is characteristic of slight obstruction, dilatation of severe or nearly complete obstruction, for in the latter condition the muscular coat becomes paralyzed and undergoes passive dilatation. Hard fecal masses are formed above the obstruction, and these in turn give rise

to small stercoral ulcers in the mucous membrane. The irritation may cause periodic attacks of catarrhal inflammation, so that an alternation of constipation and diarrhea is highly suggestive of chronic obstruction, usually carcinomatous. Chronic malignant obstruction may at any time become acute owing to inflammatory changes at the site of the stricture with swelling of the mucous membrane.

**Meconium Ileus.**—A remarkable form of ileus certain to puzzle the uninitiated occurs in the new-born. There is no narrowing of the bowel, but the lumen is blocked with thick meconium, and the wall may give way as the result of a "blow-out" following on the first feeding. In one case reported from my laboratory by Sara Meltzer the peritoneal cavity was filled with material so thick and tenacious as to suggest mucilage. In a number of cases there has been congenital stenosis of the opening of the pancreatic duct, with dilatation of the duct system and atrophy and fibrosis of the parenchyma (Kornblith and Otani). Farber (personal communication) observed this pancreatic lesion in twins, both of whom died of meconium ileus. In some cases the basis of the condition is an internal obstruction of the pancreatic duct system by inspissated secretion, the lesion which in later infancy is responsible for the picture known as cystic disease of the pancreas (Farber).

### HIRSCHSPRUNG'S DISEASE

This is a congenital idiopathic dilatation of the colon. The pelvic colon and sometimes the entire large intestine are enormously dilated and hypertrophied. The lower part of the rectum is rarely involved. The hypertrophy is due to great thickening of the circular muscular coat, but is probably not a primary condition. Chronic inflammatory changes in the mucosa and submucosa together with stercoral ulcers are due to the great accumulation of fecal matter in the sigmoid. The bowel is evacuated at long intervals of days or weeks, when a huge quantity is passed. The abdomen is greatly distended. There are countless theories to account for this obscure condition, but it may be regarded as a form of *achalasia* or inability of the circular fibers at the junction of the sigmoid and rectum to relax. A similar condition is seen at the junction of esophagus and stomach (cardiospasm) and the junction of pharynx and esophagus. The *achalasia* probably has a neurogenic basis, being due to hyperactivity of the sympathetic innervation to the circular muscle in the upper part of the rectum, and future treatment, surgical and otherwise, promises to be along this line. The dilatation and hypertrophy are results of the continued closure of the sphincter.

### CELIAC DISEASE

This is a disease of young children characterized by an inability to absorb fats from the intestine. It is also known as *idiopathic steatorrhœa* (outpouring of fat), *Gee's disease*, *non-tropical sprue*, and *intestinal infantilism* (marked impairment of development). It may be regarded as the infantile analogue of tropical sprue, a deficiency disease characterized by great wasting of fat, fatty stools, disturbance of calcium metabolism, and severe anemia. Celiac disease appears to be due to a disturbance of gastro-intestinal function resulting in deficient absorption of one or more vitamins. The name, meaning relating to the abdominal cavity (*kōilia*, belly), indicates the vagueness of our knowledge of the condition before recent biochemical investigation. The stools which are very bulky are loaded with fat, and are white, soft, frothy and foul-smelling due to excessive fermentation. There is a high fecal output of calcium and in consequence osteoporosis and rickets are common, together with low blood calcium and tetany. Anemia is a marked feature; it is usually of the hypo-

chromic type, but occasionally becomes hyperchromic and macrocytic late in the disease.

**Intestinal Lipodystrophy.**—This very rare condition was first described in 1907 by Whipple, and is therefore known as Whipple's disease. The essential lesion is a deposit of lipids, for the most part neutral fat, in the mucosa of the small intestine and the mesenteric lymph nodes. Grossly the mucosa is flecked with minute yellowish deposits, whilst microscopically the fat is contained in dilated lymph spaces of the enlarged villi and submucosa, in mononuclear phagocytes, and in occasional multinucleated giant cells. The chief clinical features are asthenia, anemia, arthritis, steatorrhea and abdominal distention in a middle-aged or elderly person. The disease usually proves fatal.

### MESENTERIC THROMBOSIS AND EMBOLISM

Thrombosis of the mesenteric vessels is much commoner than embolism. It may be arterial or venous. The arterial type is much more rapidly fatal and accompanied by gangrene of the bowel. Venous thrombosis is more frequent as might be expected, the veins being likely to contain intestinal toxins and bacteria. In the venous type the onset and course are slow, the result is often hemorrhagic infarction without gangrene, blood is always present in the stool, and spontaneous recovery is possible.

The result both of arterial thrombosis and embolism is *infarction of the bowel*. The superior mesenteric is usually involved. When the inferior mesenteric vessels are occluded the result is less serious, because they establish communication with the superior mesenteric vessels above and the hemorrhoidal vessels below. The infarct is of the red or hemorrhagic variety, and usually occurs in the ileum or lower part of jejunum. The infarcted segment is sharply limited as a rule, thick, and darker red in color. Gangrene may occur, particularly in arterial obstruction. The wall of the bowel is stuffed with red cells, dark blood fills the lumen, and there may be blood in the peritoneal cavity. The hemorrhage may be confined to the mucosa. Sometimes no occlusion of the vessels can be found.

The *symptoms* are extremely acute in embolism or arterial thrombosis, much less so in venous thrombosis. In the acute cases the first symptom is sudden severe *abdominal pain*, due to spasm of the bowel from sudden ischemia. *Blood in the stools* is highly significant. At first there may be diarrhea, but soon there is evidence of complete obstruction due to *paralytic ileus*. If gangrene of the bowel occurs it leads to *general peritonitis*, which rapidly proves fatal.

### HEMORRHOIDS

Hemorrhoids or piles is a condition in which the poorly supported hemorrhoidal veins become varicose and hypertrophied. *Internal piles* involve the superior hemorrhoidal veins and are covered by the mucous membrane of the rectum; *external piles* involve the inferior hemorrhoidal veins and are covered by skin. The *causes* are central and local. *Central* causes are cirrhosis of the liver (portal obstruction) and cardiac weakness. *Local* causes are constipation (causing straining at stool with dilatation of the veins), carcinoma of the rectum, and outside pressure from enlarged uterus, enlarged prostate, etc. *Every case of piles should first be examined for cancer of the rectum*, because cancer of the rectum can often be completely removed in the early stage. Some of the cases give a hereditary history.

The pile consists of a cluster of greatly dilated venules and may resemble a cavernous angioma. It is covered by mucous membrane or skin. Infection is frequent with accompanying phlebitis and thrombosis, known as an "attack of the piles." The thrombus may become fibrosed, a condition of spontaneous recovery. In rare cases the infected thrombus may become broken up and form septic emboli which are carried to the liver and there form abscesses. The tissue around the pile becomes fibrosed, and is often infiltrated with

chronic inflammatory cells. Apart from the attacks of thrombophlebitis the principal symptom is repeated hemorrhage during defecation, which may lead to a marked secondary anemia.

### MELANOSIS COLI

This condition is described in Chapter II. Granules of melanin pigment are found in the large mononuclear cells in the mucosa, but not in the epithelium. The condition is often associated with chronic intestinal stasis, especially carcinoma of the bowel. The pigmentation is usually limited by the ileocecal valve, but the appendix may be pigmented while the colon remains free. Marked pigmentation where the black color can be seen shining through the wall of the bowel is rare, but slight grades are common. The melanin is probably formed by the disintegration of proteins in intestinal stasis.

### CONGENITAL ANOMALIES OF THE INTESTINES

The commonest anomaly is Meckel's diverticulum, which has already been described. Other diverticula (duodenal, intestinal) may possibly have a congenital basis, but this is doubtful as they are met with late in life. There may be *stenosis* or actual *atresia* of the bowel. The common site of atresia is the lower end of the rectum, where the condition is known as *imperforate anus*. The anus is represented by a dimple of the skin, which is separated from the lower end of the rectum sometimes by a thin membrane, sometimes by a considerable interval filled with fibrous tissue. There may be congenital obliteration of the second part of the duodenum, and much more rarely at the lower end of the ileum.

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## CHAPTER XXI

### THE LIVER AND GALL-BLADDER

#### THE LIVER

**Descriptive Outline.**—The description of the liver includes its size, shape, weight, color, and consistence. The *size* is very constant in health, but as the result of disease it may be much increased (tumor, amyloid) or diminished (cirrhosis). The *shape* may be distorted by disease (syphilitic scars, etc.) or by Riedel's lobe, a tongue-like process occasionally extending downward from the lower margin of the liver external to the gall-bladder. Grooves are not infrequently seen running across the upper surface of the right lobe in an antero-posterior direction; they are probably caused by folds in the diaphragm which occupy them. A pressure groove (tight-lacing in women, rigid leather belt in working men) may pass transversely across the right lobe. The *weight* is 1400 to 1600 grams in the male, 1200 to 1400 grams in the female. The *color* is a dark reddish-brown or chocolate, but the under surface is often of an indigo color due to the postmortem action of  $H_2S$  liberated from the large bowel on the iron pigment in the liver, with the production of sulphide of iron; there may be greenish staining by bile from the gall-bladder. The common pale and sometimes red patches under the capsule (pseudo-infarcts) must not be mistaken for true infarcts, which are extremely rare. The *consistence* is that of a soft solid, but the liver is friable and easily lacerated. When placed on a flat surface the dome-like curve of the upper surface becomes greatly flattened; any softening of the liver (fatty degeneration) will increase the flattening, any increase in consistence (amyloid) will prevent it.

There is one point in the microscopic appearance worthy of note. The ordinary microscopic picture of liver cells is that of cells starved or depleted of glycogen, because the sick person has eaten nothing for a number of hours before death. In sudden accidental death the cells have a foamy vacuolated appearance, in reality the normal picture of a healthy liver but apt to be mistaken by the unwary for an indication of disease; this is due to the presence of glycogen which is dissolved out by a watery fixative such as formalin. (Fig. 256.) The liver cell nuclei do not normally contain glycogen, but glycogen infiltration of the nuclei is quite common (Chippis and Duff). Empty-appearing or vacuolated nuclei with a peripheral arrangement of chromatin indicate a high glycogen content. Severe degrees of infiltration are infrequent, being commonest in diabetes mellitus, and occasionally present in a variety of other conditions.



FIG. 256.—Glycogen in liver cells (pale and vacuolated).  $\times 500$ .

### NECROSIS OF THE LIVER

In the liver the ordinary pathological conditions such as inflammation, tuberculosis and syphilis are of little importance. Necrosis of liver cells, on the other hand, is of the greatest significance. The necrosis may be divided into: (1) *diffuse necrosis*, in which all the cells in groups of lobules are affected, as in acute yellow atrophy; (2) *zonal necrosis* in which only the cells of a certain area in each lobule are affected; and (3) *focal necrosis* in which small areas of no uniform distribution are affected, as in severe bacterial infections such as streptococcal and typhoid. Zonal necrosis may be (a) *central*, this being the commonest type; (b) *mid-zone*, well seen in yellow fever; and (c) *peripheral*, as in eclampsia. From the clinical standpoint by far the most important variety is diffuse necrosis.

The characteristic reaction of liver cells to an injurious agent is necrosis. This may be called with equal truth either hepatic necrosis or hepatitis. The liver cells in comparison with other cells in the body are always living on the dangerous edge of things, for they exist in a condition of partial anoxia owing to the fact that their main source of blood is venous in origin. When the injury is slight and transient the dead cells are quickly removed and replaced by new liver cells, because no organ has greater power of reproduction. But when the injury is severe or prolonged there is likely to be a proliferation of fibroblasts resulting in fibrosis, which in the liver is known as cirrhosis. These two processes are as closely interwoven as inflammation and repair. The term hepatitis is often used for convenience to describe all stages of the process from necrosis to healing by fibrosis.

The *causes* of hepatic necrosis are many and varied. Our knowledge regarding them is based partly on experimental work on animals, partly on clinical observations on man. It is hardly necessary to remark that we know much more about the former than the latter. Necrosis of liver cells may be produced by means of poisons and by dietary deficiency. It is obvious that all poisons absorbed from the intestinal canal must pass through the liver. One of the functions of the liver is to detoxify these poisons, but the hepatic cells may be seriously damaged in the process. Similarly all the elements of the diet are first dealt with by the liver. It is now realized that a deficiency or imbalance of various of these elements may completely upset the delicate mechanism of the complex chemical factory which each liver cell represents. There is therefore a toxic hepatitis and a deficiency hepatitis, and these are frequently combined.

*Toxic hepatitis* (necrosis) may be produced by drugs (arsphenamine, chloroform, cinchophen present as an analgesic in many proprietary cures for rheumatism), poisons used for suicidal or homicidal purposes (phosphorus, mercury), and substances used in technical and manufacturing processes (carbon tetrachloride, tetrachlorethane, and trinitrotoluene). The action of these various substances can be observed both in the animal and in man. Bacteria and their toxins can also



produce necrosis, but this is seldom or never massive. An important example of necrosis, to be considered presently is seen in the condition known as infective epidemic hepatitis, now known to be due to a filterable virus. It is also believed that certain unknown toxins of metabolic origin may produce extensive necrosis in man in such conditions as acute yellow atrophy, but this is pure speculation, and may be entirely erroneous.

Experimental toxic hepatitis has been studied by a number of workers (Cameron and Karunaratne, Hinsworth and Glynn). Much depends on the size of dose and the length of time that the poison acts. When rats are given a *single* dose of a chemical poison such as carbon tetrachloride, chloroform or phosphorus, or a bacterial toxin, illness develops in a few hours, reaches its height in twenty-four to forty-eight hours, followed by complete recovery in one to two weeks if the animal survives. Within twenty-four hours zonal necrosis develops affecting every lobule, central in type with some poisons (chloroform and carbon tetrachloride), peripheral with others (phosphorus). The dead cells are removed in a few days, and at the end of a fortnight the liver appears normal. When, however, large doses are given at short intervals portal cirrhosis develops similar to the type seen in man.

*Deficiency hepatitis*, using the term to indicate hepatic degeneration, may be of various kinds and due to a variety of deficiencies. These changes fall into the groups of fatty infiltration, necrosis and fibrosis, one or more of which may be present in any given instance.

Lack of lipotropic factors in the diet leads to the accumulation of fat in the liver (see page 22). The formation of phospholipids is necessary for the normal transport of fat, and thus the prevention of fatty infiltration of the liver. Choline plays an essential part in the formation of phospholipids, and is therefore one of the principal lipotropes. So is the sulphur-containing amino-acid methionine, which provides methyl groups for the synthesis of choline. The accumulation of fat in the liver cells may be so great as to lead to necrosis. Absence of methionine and of cystine, another sulphur-containing amino-acid, results in hepatic necrosis in the experimental animal. The necrosis which follows the prolonged administration of a low protein diet is due to the absence of the essential sulphur-containing amino-acids. These dietary substances protect the liver against the action of toxic agents such as chloroform, carbon tetrachloride, trinitrotoluene, and arsphenamine. The B vitamins also appear to be of value. In chronic alcoholism the diet is nearly always grossly deficient in the various protective food substances mentioned above. This is also true of races, such as the African Bantu, in whom liver cirrhosis (and carcinoma) is particularly prevalent. In this connection it may be noted that rats kept for a long period on a choline-deficient diet develop carcinoma of the liver in a considerable number of cases (Copeland and Salmon). It is evident that dietary deficiency and toxic factors may work together. Thus infectious hepatitis is more fatal in pregnant women, in whom the lipotropic factors are sidetracked to the fetus. This combination may

possibly play a part in the production of eclampsia. These considerations have led to the adoption of a high protein-low fat diet reinforced with B vitamins and sulphur-containing amino-acids in the treatment of infectious hepatitis and the hepatitis caused by arsenicals and other toxic agents.

In deficiency hepatitis there is a massive necrosis affecting all the cells of one or many lobules. There is always a latent period of several weeks, at the end of which illness suddenly develops and the animal may be dead in a few days. The pathological picture is similar to acute yellow atrophy in man. If the animal survives a condition of nodular hyperplasia develops, areas of necrosis alternating with areas of regenerated liver cells. The necrotic cells are removed and replaced by dilated sinusoids; these in turn give place to broad fibrous scars surrounding regenerated nodules of liver cells, a condition of cirrhosis. In some cases cirrhosis may occur independently of necrosis, due apparently to direct stimulation of the fibroblasts. The two chief differences between toxic and deficiency hepatitis are the time element (hours in the former compared with weeks in the latter), and the fact that in toxic hepatitis there is complete recovery after a single attack, whereas in deficiency necrosis scarring follows even the mildest attacks. When, however, small doses of poison are given repeatedly, cirrhosis results.

It will be observed that deficiency hepatitis in the experimental animal is characterized by acute massive necrosis closely resembling acute yellow atrophy in man and progressing to a condition of scarring similar to that of nodular hyperplasia, whereas in toxic hepatitis there is acute zonal necrosis followed by portal cirrhosis.

To apply these clear-cut experimental results to the problems of hepatic necrosis and cirrhosis in man is difficult if not impossible, but they form a valuable background for thinking about the human disease. It seems quite probable that the two factors, toxic and deficiency, may be combined, the toxin either uniting with the amino-acids or increasing the demand for protein beyond the margin of safety. Thus in poisoning by trinitrotoluene and cincophen there is a latent interval of several weeks, and the patient finally develops nodular hyperplasia, features corresponding to experimental dietary necrosis rather than toxic necrosis.

*Acute Necrosis (Acute Hepatitis).*—By far the commonest form of this condition is that known as *acute infectious hepatitis*. This may occur in sporadic or epidemic form, the latter being known as epidemic hepatitis. The sporadic cases have in the past been called catarrhal jaundice. The epidemic form was extremely common among the troops in World War II. The cause is a filterable virus, which is excreted in the stools. A similar form of hepatitis associated with jaundice may follow the administration of pooled supposedly normal human serum, of mumps convalescent serum, of yellow fever vaccine, and of arsphenamine (syringe contaminated by ieterogenic agent from blood of other patients). It is believed that in all these cases a virus is the causal

agent. As the incubation period is around one hundred days compared with an average of thirty days in infective hepatitis it must not be assumed that an identical virus is responsible in the two groups of cases. The mortality of epidemic hepatitis is low (0.2 to 0.4 per cent), but the morbidity is high. The incubation period is remarkably long, usually a month, often longer. Jaundice is a characteristic feature and hemorrhages are frequent. The spleen is enlarged in most of the cases. Ascites was present in most of Lucké's fatal cases, due probably to low plasma proteins caused by the damage to the liver. In the brain there was acute degeneration of the ganglion cells (a characteristic virus lesion) and a mild meningo-encephalitis in 15 per cent of cases.

The lesions in 125 fatal cases have been analyzed in a notable paper by Lucké. Valuable information on the condition of the liver in those cases which proceed to recovery is afforded by studies on aspiration biopsies by Roholm and Iversen and by Dible. The liver is enlarged in the early cases, but later, especially in the fatal cases, it may shrink rapidly. By the end of the second week there is marked dissociation of the liver cells, so that the trabecular arrangement is disorganized although the lobular structure may be preserved. The parenchymal cells are of unequal size, their borders indistinct, and their cytoplasm granular or vacuolated. The glycogen content is not diminished. The nuclei show various forms of degeneration. Amitotic division is frequent, whereas mitosis is rare. Roholm and Iversen point out that a comparison of biopsy and autopsy material suggests strongly that the complete necrosis of liver parenchyma observed postmortem may be a phenomenon largely due to autolysis occurring after death. By the end of the fourth week regeneration is discernible, and the trabecular arrangement is once more established. The cells are more normal looking. There is, however, an increase in the connective tissue, most marked in the periportal area and extending as irregular streaks between the lobules. Much of this is reticulum rather than collagen, but a certain degree of true cirrhosis may occur. When there is much destruction of parenchyma there may be a marked formation of new bile ducts. In addition to the degenerative changes described above there is a varying degree of inflammatory infiltration by mononuclear cells. In concluding this account of what may be called acute benign hepatitis (catarrhal jaundice) it must be emphasized that complete restoration to normal is the rule. In the fatal cases large areas of liver cells may be destroyed, and the liver may be coarsely nodular as the result of regeneration of the remaining parenchyma.

At the opposite end of the scale from benign hepatitis there is the condition known as *acute yellow atrophy*. This purely descriptive term denotes the most severe and rapidly fatal form of liver necrosis. Acute yellow atrophy and epidemic hepatitis may be regarded as two extremes of the same process. Catarrhal jaundice, as Eppinger has put it, may be acute yellow atrophy in miniature. There is at present, however, no proof that the two conditions are due to the same etiological agent. It is much commoner in women, and some of the most

fulminating cases occur as a complication of the later months of pregnancy, where there may be an element of dietary deficiency due to diversion of protein to the fetus. It may, however, occur in men and even in children. The onset is sudden and the course very acute, with vomiting, profound jaundice, appearance of bile in the urine, diminution of the liver dulness, delirium, coma, and death. Crystals of leucine and tyrosine are found in the urine.

The *liver*, as the name of the disease indicates, is atrophic and yellow. It may be one-half the normal size, the rest having been destroyed. The capsule is wrinkled on account of the shrinkage, and the liver is very soft. At first the color is bright yellow, but later it becomes red as the necrotic cells disappear (red atrophy). The yellow

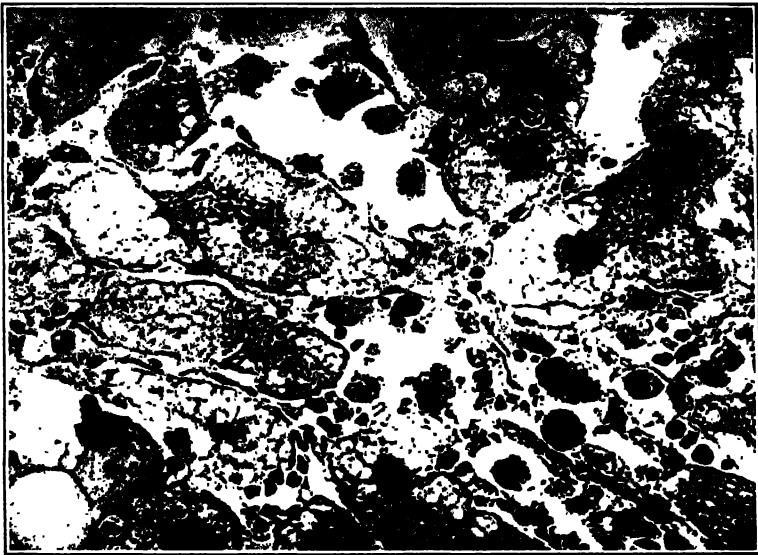


Fig. 257.—Acute yellow atrophy of the liver. There is an extreme degree of destruction of the liver cells.  $\times 350$ .

color is due to the necrotic cells being stained with bile, the red color is caused by the increased vascularity of the later stages. If death occurs very early the liver is completely yellow. The usual appearance at autopsy is a mottling of red and yellow areas. *Microscopically*, the greater part of the liver may be necrotic. The liver cells are either disintegrating or have disappeared, being replaced by granular debris. (Fig. 257.) The lobules now consist of dilated capillaries filled with blood, and it is these which give the red color to the liver in the later stages. A striking feature is the extraordinarily rapid disappearance of the damaged liver cells. The illness may only have lasted a few days, yet the liver cells may have vanished in large areas. This is not seen in the other hepatic necrosis; it is perhaps due to autolysis.

The *kidneys* are apparently acted on by the same toxin which destroys the liver, and the epithelium of the convoluted tubules may show a considerable amount of necrosis. In consequence of the renal lesions albumin and casts appear in the urine. Other *urinary changes* are due to the disturbance of the liver. The urea excreted is greatly diminished as it is no longer formed by the liver, while the amino-acids are correspondingly increased as the normal deamination which occurs in the liver is stopped. The leucine and tyrosine which may crystallize out are protein cleavage products derived from the necrotic liver cells.

*Subacute necrosis with nodular hyperplasia* is the name applied to those cases of massive necrosis which recover from one or more attacks. The patient frequently has a number of recurring attacks characterized by jaundice, epigastric pain, vomiting and fever. These symptoms may be quite mild, in which case the picture is one of catarrhal jaundice. It will be evident that there is no sharp line to be drawn between this state of affairs and epidemic hepatitis. The liver is coarsely nodular and cirrhotic, the nodules of regenerated liver tissue being often quite large. This is the condition called by Mallory *toxic cirrhosis* and by Marchand *multiple nodular hyperplasia*.



FIG. 258.—Liver in eclampsia, showing peripheral hemorrhagic necrosis.

**Eclampsia.**—In this grave complication of the later stages of pregnancy there is a hemorrhagic necrosis, usually peripheral in distribution, in about half the cases. (Fig. 258.) There may be large red splashes on the surface of the liver, so that the organ presents a striking and highly characteristic picture. It used to be thought that the liver lesions were the essential feature of eclampsia, but it is now believed that the basic changes are in the kidney.

### CIRRHOSIS OF THE LIVER

Cirrhosis of the liver has been defined by Moon as a progressive chronic inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchymal cells and proliferation of remaining cells in the direction of regeneration.

A satisfactory classification of cirrhosis is impossible, because the antecedents of the condition are unknown in the great majority of cases. Two main forms can be recognized, portal cirrhosis and biliary cirrhosis, and two lesser forms of minor importance, pigment cirrhosis or hemochromatosis and syphilitic cirrhosis.

**Portal Cirrhosis.**—This is the common form of cirrhosis. It is also known as Laennec's cirrhosis, atrophic cirrhosis, multilobular cirrhosis and alcoholic cirrhosis. The essence of the condition is destruction of the hepatic cells and their replacement by fibrous tissue. It is probable that the fibrous tissue is stimulated to proliferate by the injurious agent.

**Etiology.**—There is no one cause of portal cirrhosis, just as there is no one cause of contracted kidney. Any agent which leads to diffuse necrosis of hepatic cells can give rise to cirrhosis. The known causes of liver necrosis have already been enumerated. Some of these, such as the use of cinchophen in proprietary medicines, can produce typical portal cirrhosis. In the great majority of cases of cirrhosis no cause can be demonstrated.

It seems justifiable to distinguish two main groups as regards pathogenesis: (1) a common primary or idiopathic type due to various slow-acting agents; (2) a secondary type following one or more attacks of acute or subacute hepatic necrosis, which may be called post-necrotic cirrhosis (Karsner). The former type is more common in men, the latter is much commoner in women.

1. In the great majority of cases cirrhosis is the result of a slow long-continued necrosis, a nibbling away of hepatic cells and their replacement by fibrous tissue. The cause of this gradual destruction is uncertain. There is no history of attacks of any kind. There is little doubt that a variety of toxins, bacterial, metabolic, or even exogenous may be responsible. Anything which interferes with tissue respiration (oxidation) in the hepatic cells may give rise to necrosis and finally cirrhosis. When there is anoxia of the hepatic cells, efficient carbohydrate metabolism cannot take place, and the cells become infiltrated with fat which replaces the normal glycogen. Marked fatty infiltration appears to be an antecedent of cirrhosis in many cases, especially when alcohol is a factor (Connor). Many of the hepatic poisons, such as chloroform, ether, carbon tetrachloride, and alcohol, interfere with cell respiration in the liver, and this is followed by glycogen depletion, accumulation of fat, and eventual disintegration of the liver cells. The action of these and other agents is intensified by infection, pregnancy, and dietary deficiencies. The importance of what has been called dietary cirrhosis in the experimental animal is becoming recog-

nized (György, Rich and Hamilton, Lillie, *et al.*). Various forms of dietary deficiency are injurious to liver cells and may eventually lead to cirrhosis. Among these may be mentioned vitamin deficiency, high fat diet, and a combination of low protein and low choline. Chaikoff and his associates have produced cirrhosis in dogs by the long-continued administration of a high-fat diet. The liver cells become loaded with fat and then atrophy, this being followed by fibrosis extending out from the portal areas. Choline deficiency in animals first induces severe fatty degeneration of the liver followed later by portal cirrhosis. In rats a low protein intake associated with a deficiency of the vitamin B complex leads to liver necrosis followed by periportal cirrhosis (György and Goldblatt). Nodular cirrhosis can be produced in rats by feeding them the azo compound known as butter yellow (paradimethylaminoazobenzene) for several months (Orr). The new connective tissue thus formed is absorbed in part or completely some months after the rats are restored to a normal diet (Steinberg and Martin). In experimental work it is possible to produce cirrhosis by a combination of agents, either of which singly is without effect (Moon). The administration of chloroform followed by the intravenous injection of streptococci results in cirrhosis (Opie). It seems probable that in human cirrhosis also two or more factors may often be responsible. In chronic alcoholism there is a low intake of protein, carbohydrate and vitamins, diminished storage of glycogen, and fatty replacement of the liver cells. These conditions render the liver more vulnerable, with consequent necrosis and cirrhosis. There seems to be no doubt that alcohol can cause portal cirrhosis. The difficulty is to know how frequent a cause it is. The pathologist must not be misled by a negative history of alcoholism in these cases, for chronic alcoholics are notorious liars in respect to their drinking habits. The length of time over which a liver poison acts has an important influence on the effect, at least in the experimental animal. If the action of a chemical poison such as carbon tetrachloride is intense over a short period, the result is acute necrosis with jaundice, whereas if it is prolonged or spaced at short intervals the effect is likely to be cirrhosis, because the lobules are not allowed sufficient time for complete repair.

2. The post-necrotic type may be due to agents known to cause diffuse necrosis (cincofen, arsphenamine, trinitrotoluene) or may belong to the idiopathic group of yellow atrophies. This type has been called toxic cirrhosis (Mallory). There may be repeated attacks of jaundice with epigastric pain, vomiting and fever, attacks which are designated by the clinician as hepatitis. At each attack large groups of liver cells are destroyed. If the patient survives, these areas are replaced by fibrous tissue, whilst the remaining cells undergo compensatory nodular hyperplasia. As the result of the hyperplasia quite large nodules of new liver tissue may be formed, the multiple nodular hyperplasia of Marchand.

In actual practice it is often difficult or impossible for the pathol-

ogist to differentiate between the two types of cirrhosis, although the clinical history is usually of value. Indeed it is possible that the distinction itself may be unjustifiable, and that final simplification may be reached by the statement that hepatic cirrhosis is merely the end stage of hepatitis, its character depending on the type of injurious agent, its dose, and the time during which it operates.

**Lesions.**—The *liver* is atrophic in the later stages, but in the earlier stages it may be larger than normal. This is especially the case when the fatty changes due to chronic alcoholism are marked. In extreme cases it is only one-half the normal weight. The consistence is very firm owing to the large amount of fibrous tissue and it is usually difficult to cut. The surface of the liver has a characteristic nodular appearance (hob-nail liver), and the cut surface is correspondingly nodular. (Fig. 259.) The nodules vary much in size. Large nodules

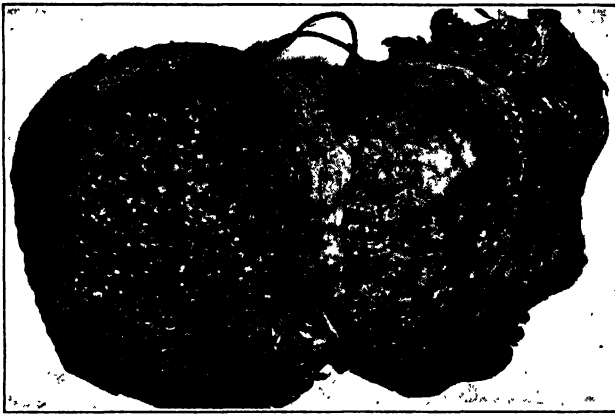


FIG. 259.—Portal cirrhosis of the liver. The external surface has a coarsely granular hob-nail appearance.

over 2 cm. in diameter suggest the post-necrotic type cirrhosis, and these may be so large as to produce distortion of the liver. In ordinary cirrhosis the nodules are small (hob-nail liver) and the surface may be merely granular. The color varies. The islands of liver tissue may show no change from the normal, they may be yellow from fatty changes, or green due to staining with bile. There is often a general brownish or tawny coloration (to which the name of cirrhosis was originally due) caused by the deposition of iron pigment.

*Microscopically* the earliest change is a proliferation of the connective tissue in the portal space. Normally there is sharp delineation of this space, but in cirrhosis the boundary is broken by proliferation of fibroblasts between the degenerated peripheral cells. As the disease advances groups of liver cells of very varying size are separated by broad strands of fibrous tissue. The islands of liver cells may resemble lobules, but this appearance is fictitious; there is no true lobular



arrangement, for there is no central vein in the center of the islands, which for the most part represent new formations due to regenerative hyperplasia. The portal vein does not drain into the new nodules, which get their blood supply from the hepatic artery. The salient feature is thus loss of hepatic architecture. The nodules are composed largely of new cells which show irregularity of size and arrangement. Between the nodules the liver cells have disappeared. Occasionally some of the degenerating cells contain a peculiar hyaline material staining deeply with eosin; this appearance used to be considered as characteristic of alcoholic cirrhosis (Mallory), but this view has had to be abandoned. The connective tissue forms broad bands between the islands of liver cells, and may be young and cellular

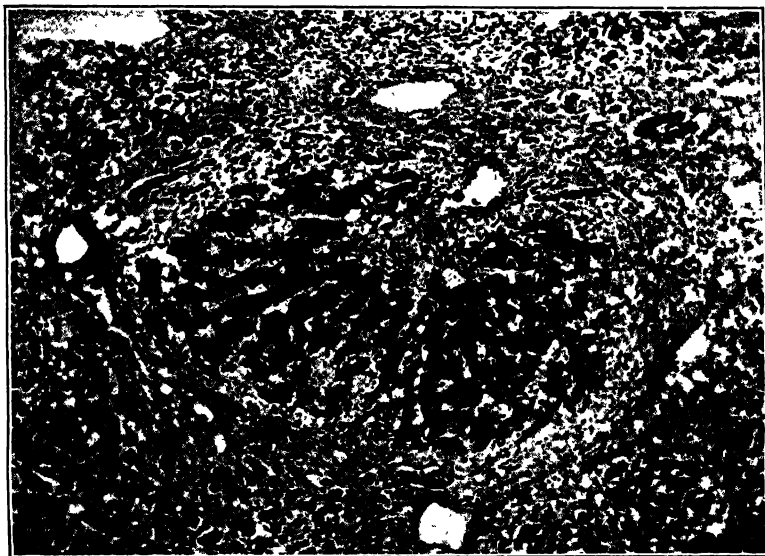


FIG. 260.—Portal cirrhosis of liver. Great replacement of liver cells by fibrous tissue, with formation of new bile ducts.  $\times 50$ .

or old and fibrous. Chronic inflammatory cells are present, sometimes in large numbers, but the chief feature is the greatly increased number of bile ducts. Cords of young liver cells may simulate new bile ducts. There is evidently a proliferation of biliary epithelium which establishes connection with the new groups of liver cells. Jaundice only appears late in the disease and even then it is seldom marked.

Typical lesions of portal cirrhosis are found in Banti's disease and in progressive lenticular degeneration (Wilson's disease).

Testicular atrophy is a common finding in hepatic cirrhosis. It is much more frequent in those below the age of fifty years than in those above that age. It has been suggested from experimental evidence that there is failure of normal inactivation of estrogens by the liver,

and that this results in atrophy of the testes (Morrione). The urine from patients with cirrhosis of the liver contains increased amounts of free estrogens, and it is well known that administration of estrogens leads to testicular atrophy.

**Biliary Cirrhosis.**—In this form of cirrhosis the etiological factor which damages the liver cells and stimulates the connective tissue to proliferate comes by way of the bile ducts. It is a good deal less common than the portal form. It is usually due to obstruction of the bile passages, hence is known as *obstructive biliary cirrhosis*. Some cases where there is no obstruction may be attributed to biliary infection.

The chief causes of biliary obstruction are cancer of the head of the pancreas, stone in the common bile duct, and benign stricture of the duct. Cancer of the head of the pancreas is likely to cause rapid dilatation of the hepatic ducts rather than cirrhosis, which is a slow process. Congenital obstruction of the bile passages in children leads to the obstructive type of cirrhosis.

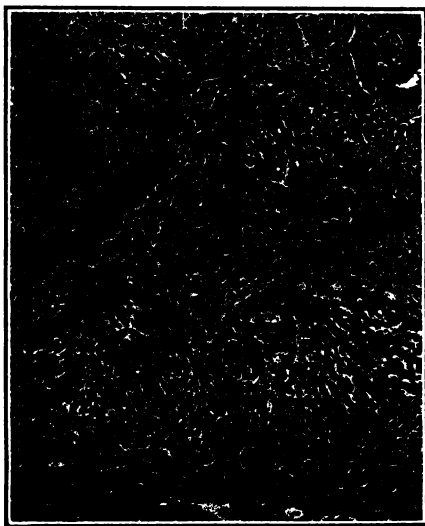


FIG. 261.—Biliary cirrhosis. The cirrhosis is monolobular in type. Numerous bile ducts in connective tissue.  $\times 50$ .



FIG. 262.—The effect of biliary obstruction. The bile canaliculi are distended with bile and the liver cells are disintegrating.  $\times 600$ .

The *liver* is usually of normal size, but it may be enlarged. The surface is smooth or very finely granular and the whole liver may be stained an intense green. The bile ducts are dilated and tortuous and new ducts appear to be formed. The connective tissue in the portal areas is increased and infiltrated with chronic inflammatory cells. This connective tissue encircles the lobules, so that the cirrhosis tends to be monolobular in type (Fig. 261). The bile canaliculi in the interior of the liver cells are distended with thick bile to such an extent that the liver cells may be disintegrated (Fig. 262); they seem

to burst, the canaliculi are ruptured, and the inspissated bile is seen between the liver cells and the walls of the sinusoids. There is marked jaundice but no ascites. The spleen may be enlarged.

Sometimes the liver presents a picture of biliary cirrhosis, but no obstruction can be demonstrated. Biliary infection may be blamed, and the lesion called *infective biliary cirrhosis*. *Hanot's cirrhosis* or *primary biliary hypertrophic cirrhosis*, a rare condition characterized by severe jaundice, a very large green liver and an unduly large spleen, may be regarded as due to intrahepatic obstruction, perhaps caused by inflammation of the finer bile ducts.

**Hemochromatosis.**—This rare condition, known also as bronzed diabetes, is not really a disease of the liver but a disturbance of iron metabolism. The liver contains enormous quantities of iron in the form of hemosiderin. The pigment is present in the liver cells, Kupffer cells and connective tissue. Owing to the continued irritation of the pigment the liver cells become necrosed and disappear, and there is a marked proliferation of connective tissue with a resulting *pigment cirrhosis*, the microscopic appearance of which is identical with portal cirrhosis. The liver is usually enlarged and of a characteristic brown color. The general question of hemochromatosis is discussed in Chapter II.

**The Relation of Symptoms to Lesions.**—Although the cirrhotic liver may show marked disorganization and actual destruction of the parenchyma of the organ, there is a remarkable freedom from symptoms of hepatic insufficiency, owing to the great margin of safety which the liver possesses. The symptoms are mainly those of obstruction, both portal and biliary.

**Portal Obstruction.**—This is the chief effect of portal cirrhosis. There is congestion of the entire portal circulation with digestive disturbances, anorexia, etc. Ascites develops owing to transudation through the walls of the mesenteric veins. The spleen is enlarged. It differs from the cardiac spleen of heart disease in being much larger but not nearly so hard. In the cardiac spleen the sinusoids are distended with blood, while in the cirrhotic spleen there is a cellular increase of the pulp and marked deposits of hemosiderin. The splenic enlargement of cirrhosis is not always due to portal congestion, for it may be present in biliary cirrhosis. It is probable that the infective or toxic agent which acts on the liver acts also on the spleen. This is apparently the case in Banti's disease.

A *collateral circulation* is established with the systemic circulation, but this seldom proves sufficient. Moreover *varicose dilatations* are apt to develop at the points where the two circulations communicate. Three of these are of clinical importance. (1) At the lower end of the esophagus and the cardiac end of the stomach the varicosities may give way, causing severe or fatal hemorrhage (hematemesis). The injudicious use of the stomach tube may cause rupture of these veins. They are easily overlooked at autopsy because the veins collapse when the liver is removed, so that the esophagus should be examined first in a case of cirrhosis. (2) Less frequently varicosities (hemorrhoids) are formed at the junction of the inferior mesenteric and hemorrhoidal veins. (3) The epigastric veins of the abdominal wall which communicate with the veins at the hilus of the liver by way of the round ligament become dilated, and there may be a ring of varicosities around the umbilicus known as the *caput medusæ*.

The cause of the venous obstruction is not stenosis due to the contracting fibrous tissue as is commonly supposed, although it cannot be denied that this may play some part. Injection and corrosion preparations show that there is a great diminution of the total vascular bed, so that the main trunks of the portal vein are stenosed and the finer radicles disappear. The reason for this appears to be the great destruction of the liver parenchyma which is the essen-

tial lesion in cirrhosis, followed by gradual obliteration of the now functionless radicles. It is true that new groups of liver cells are formed, but these are not true lobules, and it can be seen from injection preparations that they are completely devoid of venous channels.

There may be marked *hypoproteinemia* in portal cirrhosis. This causes a low serum colloid osmotic pressure, which probably accounts for the edema which may develop and partly at least for the ascites.

*Biliary Obstruction.*—Jaundice is the great symptom of obstructive biliary cirrhosis, the bile being unable to escape from the bile ducts and accumulating in the blood. Cases of portal cirrhosis often develop jaundice in the terminal stages, but it is seldom severe. It may be explained by the extreme disorganization and distortion of the normal architecture of the liver. Indeed it is to be wondered at that jaundice is not a more marked feature of portal cirrhosis.

### ABSCESS OF THE LIVER

An abscess may be caused by infection reaching the liver by way of (1) the hepatic artery, (2) the portal vein or (3) the bile duct.

(1) *Hepatic artery infection* is a manifestation of pyemia, often complicating ulcerative endocarditis. Large numbers of small, even microscopic, abscesses are scattered through the liver. The condition is a terminal one, and death occurs before the abscesses have time to attain any size.

(2) *Portal vein infection* is usually due to septic embolism from a focus of suppuration in the appendix, or sometimes in the stomach or intestine. It is a portal pyemia, so that the abscesses are multiple, being most numerous in the right lobe. They are likely to become much larger than those of hepatic artery infection, as the patient has more chance of living longer. Occasionally there is direct extension of the inflammation from the septic focus in the gastro-intestinal tract along the portal vein to the liver, a condition of suppurative, *pylephlebitis* (*pyle*, a gate). The portal vein is filled with a soft infected thrombus, and when it is slit open it can be followed down to the original source of the infection.

*Amœbic abscess* or tropical abscess is a special example of portal vein infection. It is a common complication of amœbic dysentery, the amœbæ being carried from the intestine to the liver by the portal circulation. The abscess may be single or multiple. The common site of the solitary abscess, which may attain a great size, is the upper part of the right lobe causing upward displacement of the right dome of the diaphragm. The contents are viscid and chocolate-colored, but are necrotic rather than purulent unless secondary infection occurs. It may rupture into the peritoneum or lung. The condition is often a very chronic one.

(3) *Bile-duct infection* causes cholangitic abscesses. They are associated with calculus obstruction in the ducts or suppuration of the gall-bladder. The abscesses are multiple and of considerable size, and the bile ducts are filled with pus.

## SYPHILIS OF THE LIVER

Syphilis of the liver may occur in two forms, congenital and acquired. The congenital lesions are usually diffuse, the acquired are localized.

**Congenital.**—This form occurs in a child the subject of congenital syphilis. In the early stages the liver is enlarged; later it may be contracted. In Levaditi preparations the liver is found to be swarming with spirochetes, which are distributed diffusely through the entire organ. This serves to explain the lesion which is known as *syphilitic cirrhosis*, and takes the form of a fine diffuse fibrosis which penetrates the lobules and may separate the liver cells. (Fig. 263.) The spirochetes injure the fibroblasts, and these proliferate to such a degree that there is a secondary atrophy of the liver cells. This is the opposite of what occurs in ordinary cirrhosis. As the fibrous tissue contracts the liver tends to become atrophic. Its surface remains smooth. In addition to the syphilitic cirrhosis small gummata may be formed.



FIG. 263.—Syphilitic cirrhosis. The individual liver cells are separated by fine connective tissue.  $\times 400$ .



FIG. 264.—Gumma of liver.

**Acquired.**—The lesion of the acquired form is the tertiary gumma of which there may be several. (Fig. 264.) They may be of considerable size. The left lobe tends to be more involved than the right. There may be tumor-like masses on the surface. As the gummata heal abundant scar tissue is formed, and when this contracts deep fissures are produced. These fissures divide the liver into irregular lobes, so that sometimes a remarkable degree of deformity is produced which is absolutely characteristic of the condition. Such a deformed and scarred liver is called *hepar lobatum*. (Fig. 265.)

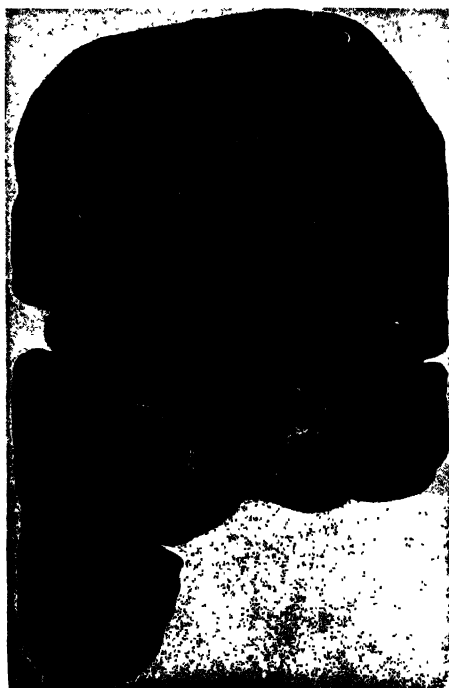


FIG. 265.—*Hepar lobatum*.

### TUBERCULOSIS OF THE LIVER

This may take two forms. (1) *Miliary tubercles* are scattered through the liver in general miliary tuberculosis. They are usually found in the region of the portal tract. (2) The solitary tubercle or *tuberculoma* is a rare condition in which a large caseous mass is formed which is easily mistaken for a gumma. Indeed the differentiation may not be possible unless the tissue is stained for tubercle bacilli.

### ACTINOMYCOSIS OF THE LIVER

The infection usually spreads from a primary focus in the cecum or appendix. Secondary abscesses are formed in the liver. These at first are arranged in small groups so that the affected area has a loculated or honeycomb appearance

which is very characteristic. In some cases it resembles a sponge full of pus. Later large abscesses are formed containing the familiar sulphur granules in which the mycelia can be demonstrated.

### TUMORS OF THE LIVER

Although the liver has such remarkable powers of hyperplasia, primary tumors both innocent and malignant are quite rare. Secondary tumors are very common, because all the blood from the gastrointestinal canal and pancreas passes through the liver, and it is supplied in addition by the hepatic artery.

**Primary Carcinoma.**—Primary cancer is as rare as secondary cancer is common. Before diagnosing a tumor as primary carcinoma, every other possible source of growth must be excluded. There are two forms of primary carcinoma of the liver: (1) *hepatoma* or liver-cell carcinoma; this is the usual variety; (2) *cholangioma* or bile-duct carcinoma. In typical cases the differentiation is very easy, but in atypical cases it is very difficult. In a series of 49 cases of primary carcinoma of the liver reported by Wilbur, Wood and Willett from San Francisco, 92 per cent were hepatomas and only 8 per cent originated from the bile ducts. The sex incidence was striking, for 96 per cent were in males. Nine of the patients were under forty years of age, and in one an abdominal mass was discovered three days after birth. In 12 cases there was gross bleeding into the peritoneal cavity.

**Hepatoma.**—There may be one large tumor with a few small out-lying nodules, or more rarely multiple small nodules are scattered throughout the liver without any large primary growth. The massive tumors are soft, necrotic, and often show hemorrhage. When the growths are multiple there has usually been spread through the liver by the portal vein, for invasion of the vein is common. In some cases it appears probable that the tumors are of multicentric origin. This is especially so with the small multiple type of growth. The intervening portions of the liver may be very firm owing to portal cirrhosis which is commonly associated with primary carcinoma, and may give the liver a finely nodular appearance. *Microscopically* the tumor consists of liver cells very irregular in size and arrangement. They are arranged in interlacing strands, but sometimes show an attempted alveolar or even adenomatous formation which is easily confused with that of bile-duct carcinoma. Multinucleated giant cells may form a striking feature; indeed some of the largest carcinomatous cells occur in this tumor. (Fig. 266.) Cirrhosis is often prominent in the remaining parts of the liver; it is of the portal type. It is probable that the cirrhosis is primary, and that the tumor arises from the associated hyperplastic nodules.

Primary cancer of the liver has a curious geographic distribution. It is very rare in Europe and America, but it is very common in the natives of the Far East, especially some parts of China and Malaya, and of South Africa. Indeed in Java and other large centers it is the commonest of all forms of carcinoma. Experimental carcinogenesis

suggests a probable explanation of the mystery. Investigators in Japan induced primary cancer of the liver in mice and rats by adding certain azo dyes, such as butter yellow, to the diet (Sasaki and Yoshida). European and American workers failed to confirm these results. The reason for this was found to lie in the diet. The Japanese animals were fed on rice and carrots, whereas the European and American animals were fed largely on wheaten cereals. When the latter animals were fed on the Japanese diet, the butter yellow produced cancer of the liver. It was then found



FIG. 266.—Hepatoma. The very large cells are characteristic of this tumor.  $\times 200$ .

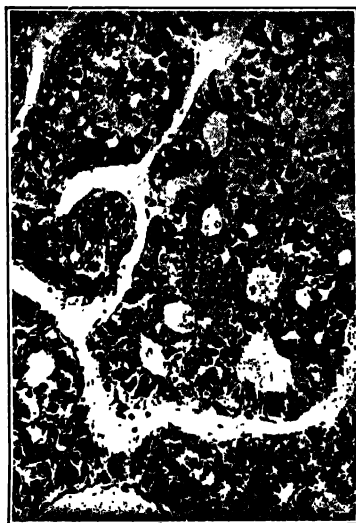


FIG. 267.—Cholangioma. The tumor cells in places are arranged around ducts.

that the protective factors in the diet were casein and riboflavin (Sugiura and Rhoads). It may be noted that when rats are kept for a long period on a choline-deficient diet a considerable proportion of them develop carcinoma of the liver, either hepatoma or adenocarcinoma (Copeland and Salmon). It is highly probable that the explanation of the peculiar geographic incidence of human liver cancer is a matter of diet.

**Cholangioma.**—Bile-duct carcinoma is less common than hepatoma and less often associated with cirrhosis. The tumors are multiple, and the liver is enlarged and stained with bile. The *microscopic appearance* is that of an adenocarcinoma in typical cases, the lining cells resembling those of the bile ducts. (Fig. 267.) Giant cells are seldom seen. In the more atypical forms the structure resembles that of a hepatoma.



**Symptoms.**—The symptoms of primary carcinoma of the liver are often due as much to the cirrhosis as to the tumor. Jaundice and ascites are common. A very rapidly recurring ascites suggests malignant invasion of the portal vein. Fever is present in over 10 per cent of cases. It may be compared with the fever of gumma of the liver, and in both cases seems to depend on a mass of necrotic material in the liver.

**Secondary Carcinoma.**—Secondary carcinoma of the liver is very common. The spread may be: (1) from the gastro-intestinal tract by way of the portal vein, (2) by the systemic circulation (hepatic artery), (3) by the lymphatics, (4) by direct spread from the gall-bladder, stomach, or pancreas. Cancer of the stomach is the most common primary site, but cancer of the breast and the lung deserve special mention. Other sites are the kidney, adrenal, uterus, and eye (malignant melanoma).

The liver may be enormously enlarged or of normal size. The tumors are multiple and are more on the surface than central in position. They vary greatly in size, are soft and necrotic, and may be yellow from necrosis, green from bile-staining, or red from hemorrhage. The superficial tumors show a falling-in of the center due to necrosis, which from the outside gives an appearance of dimpling known as *umbilication*. There is no cirrhosis.

Willis points out that invasion of the larger portal tributaries in the liver by tumor growth is responsible for the multiplicity of nodules. There may be only one metastasis in the first place, but this mechanism, which can be demonstrated by cutting the liver into thin slices, is responsible for the multiplicity. Invasion of efferent veins is an important factor in further dissemination to the lungs.

**Sarcoma.**—Primary sarcoma is extremely rare. Secondary sarcoma is not common.

**Innocent Tumors.**—An *adenoma* is very rare. It usually remains small and is composed of irregular columns of liver cells; the normal architecture of the lobule is lost. The nodules in a cirrhotic liver when large may be mistaken for adenomata. *Cavernous hemangioma* is fairly common. It is found by accident at autopsy and causes no symptoms. It forms a small red or purple area always situated on the surface and apt to be mistaken for an infarct. It consists of cavernous blood-filled spaces.

## PARASITES IN THE LIVER

**Hydatid Disease.**—The presence of hydatid cysts in the liver causes a tumor-like enlargement. It is a comparatively rare disease except in those sheep-raising countries where men come into intimate contact with dogs, *e. g.*, Australia, South America, etc. In these countries it is very common. The life cycle of *Tania echinococcus*, of which the cystic stage is the hydatid, has already been traced in Chapter VIII. The ingested embryos bore their way through the wall of the bowel, and are carried to the liver by the portal vein. Here they develop into the larval or cysticercus stage. The cyst wall is composed of a laminated membrane rather like the white of an egg, lined by a germinal layer from the cells of which daughter cysts grow. Scoleces or

heads of new individuals are formed within the cysts, and these are armed with a row of small hooklets. The nature of the cyst can be recognized from the microscopic appearance of the laminated membrane, or the presence of the tiny hooklets in the watery fluid.

The liver may be greatly enlarged, and the mass caused by the large cysts is easily mistaken clinically for a tumor. The larvæ dies out after some years, and the cyst may be converted into a putty-like mass with calcification of the capsule. Rupture may occur into the abdominal or pleural cavity, and the fluid may produce toxic effects. The fluid may be used as an antigen in a complement-fixation test or a precipitin test for the disease.

**Other Parasites.**—In tropical countries (China) *Distoma hepaticum* may invade the bile ducts and cause jaundice. *Bilharzia hæmatobia* (*Schistosoma hæmatobium*) may invade the branches of the portal vein and deposit the ova in the connective tissue of the liver. This causes a rather characteristic form of cirrhosis with areas of dense white connective tissue around the portal tracts. The condition is common among the native races, and is of interest because it may be associated with primary carcinoma.

### DEGENERATION OF THE LIVER

**Fatty Degeneration.**—So-called fatty degeneration of the liver has already been considered in Chapter II. It is really an infiltration, fat being carried from the fat depots to the liver where it fails to be metabolized for various reasons. Accumulation of fat in the liver is one of the most delicate indicators of interference with the health of the organ. It is marked in diabetes, pernicious anemia, chronic alcoholism, etc. Starvation induces the condition, thus explaining in part the frequency with which it is found in hospital autopsy material. The part played by lipotropic factors in the experimental production of accumulation of fat in the liver has already been discussed on page 22. Extensive replacement of liver cells by fat in heavy drinkers may be the cause of entirely unexpected and abrupt death (LeCount and Singer). The liver is huge, and the liver cells are represented by large fat globules. Replacement of glycogen is the probable cause of death. The fatty liver is yellow in color and greasy to the touch. The fat is either in the form of one large globule which pushes the nucleus to one side or of many tiny droplets scattered through the cytoplasm. The latter probably indicates a greater disturbance in the health of the cell.

**Amyloid Degeneration.**—Amyloid disease is described in Chapter II. The spleen and the kidney are involved as well as the liver. The liver is much enlarged, smooth, and firm and elastic in consistence. The cut surface has a characteristic translucent (waxy) look, with brown amyloid patches when treated with iodine. The essential change is an extreme hyaline (amyloid) swelling of the connective tissue, as a result of which the liver cells undergo a pressure atrophy and largely disappear. The veins and sinusoids are also compressed, yet ascites is a rare occurrence though sometimes it does develop. There is no

jaundice. In advanced cases the microscopic changes are so extreme and the replacement of liver cells so great that it is remarkable that there is so little disturbance of liver function.

**Atrophy.**—This is most marked in inanition, and in chronic starvation the liver may be quite shrunken and of a uniform brown color with loss of lobulation. In old age some atrophy is common. Pressure of a tumor, of amyloid deposits, etc., may produce local atrophy. Tight lacing (in the past) or continual stooping (occupational) may lead to the formation of grooves on its upper and anterior surface. There may be deep sagittal furrows corresponding to bulgings of the diaphragm.

**Postmortem Changes.**—The commonest change is a bluish or greenish *discoloration* of the surface, due to the action of hydrogen sulphide liberated from the intestine and similar to the postmortem discoloration of the abdominal wall. It is seen first in those parts of the liver in contact with coils of intestine. *Foamy liver* is a condition in which the organ is filled with bubbles of gas, which are produced after death by gas-forming bacilli. It may resemble a sponge. The condition is most likely to occur in wound infections with the anaerobic gas-producing bacteria.

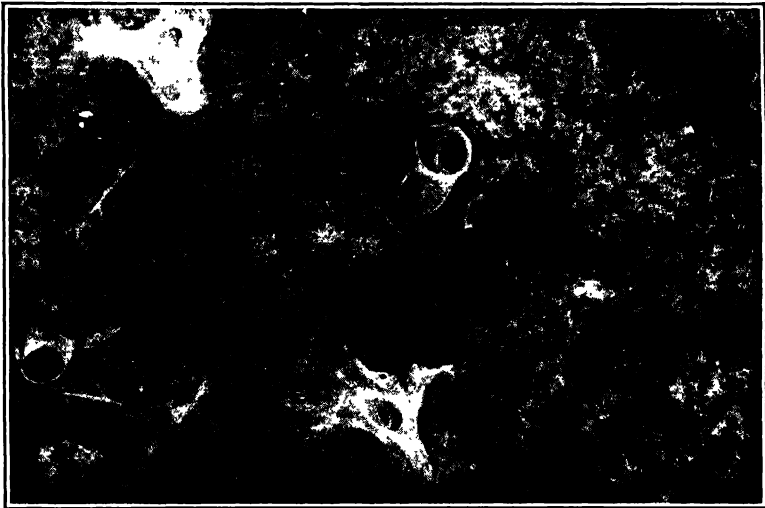


FIG. 268.—Nutmeg liver showing a combination of chronic venous congestion and fatty degeneration.

### CIRCULATORY DISTURBANCES OF THE LIVER

**Chronic Venous Congestion.**—No organ shows chronic congestion so often as the liver, because when there is any back pressure on the venous circulation it is the hepatic vein which feels it first, as it practically opens into the right auricle. The common cause is valvular disease of the heart or myocardial failure. Emphysema which narrows or obliterates the pulmonary capillaries causes distention of the right side of the heart, and this is followed by congestion of the liver.

The liver is enlarged so that it can be felt below the costal margin, firm, and as the capsule is tightly stretched it may be painful and

tender. In the later stages it may become smaller owing to atrophy of the parenchyma. The cut surface shows the characteristic appearance known as *nutmeg liver*, characterized by undue distinctness of the lobules and a mottling with dark and light areas. (Fig. 268.) The central vein and the surrounding sinusoids are filled with blood so that the center of the lobules is dark red; the periphery is pale because the cells are fatty and swollen, and the congestion of the sinusoids is much less there. *Microscopically* the central vein and the sinusoids of the central area of each lobule are so distended with blood that the liver cells may have largely disappeared owing to pressure atrophy. At the periphery of the lobule the congestion is usually much less marked, and the liver cells are fairly intact, but they show a considerable degree of fatty degeneration owing to the poor oxygenation. Owing to the disappearance of the central cells there is a condensation of the stroma, which some writers refer to as *cardiac cirrhosis*.

**Infarction.**—True infarction of the liver is a remarkably rare occurrence. Pseudo-infarcts are much commoner. The latter are generally hemorrhagic, and are really localized areas of venous engorgement, but they may be anemic. The distinction between true and false infarcts depends on the presence or absence of necrosis, so that it can only be made with the aid of the microscope. There are various reasons for the rarity of true infarcts. (1) The liver has a double blood supply from the hepatic artery and the portal vein. (2) About 65 per cent of the blood is supplied by the portal vein, and cutting off this venous blood is not likely to have the same effect on the liver cells as the loss of arterial blood; I have seen complete thrombosis of the portal vein without any apparent damage to the liver. (3) The liver cells are accustomed to a condition of relative anoxia, and they can resist temporary ischemia caused by ligation of the hepatic artery and portal vein for six to twelve hours. (4) Unnamed collateral vessels pass from the diaphragm into the liver. (5) The hepatic artery does not arise directly from the aorta. The chief causes of infarction are embolism of the hepatic artery and periarteritis nodosa affecting that vessel, both very rare conditions. The infarct tends to remain red, but it may become pale. *Traumatic infarction* is a condition in which the blood supply to a portion of the liver is cut off as the result of laceration from crushing injuries. The affected part undergoes a coagulative necrosis and has a dull yellow appearance. The condition is rare because the patient is likely to die of hemorrhage into the peritoneal cavity.

**Portal Thrombosis.**—Thrombosis of the portal vein may complicate cirrhosis and primary carcinoma. Sometimes it is the result of a chronic phlebitis. The wall of the vein usually shows evidence of sclerosis. When the main vessel is filled by a thrombus there will be very marked and rapidly recurring ascites, enlargement of the spleen, and other signs of portal obstruction.

**Hepatic Vein Thrombosis.**—This rare condition may be due to a tumor extending into the vein, to portal cirrhosis, and sometimes to no obvious cause. I have seen a case in which thrombosis followed three weeks after an abortion. The chief effects are pain and swelling of the liver and ascites.

## CONGENITAL ANOMALIES OF THE LIVER

In rare cases one lobe of the liver may be absent or the left lobe may be very small. *Riedel's lobe* is a downward prolongation of the right lobe which may be mistaken for an abdominal tumor. *Cystic liver* is probably a congenital condition, although it is usually seen in the adult. It is associated with the much commoner congenital cystic kidney, but the latter usually occurs without any cysts in the liver. Sometimes there are cysts in the pan-

creas. The cysts in the liver may be few and small, or the whole liver may be studded with large and small cysts so that the organ is greatly enlarged. In this case there will be great pressure atrophy of the liver parenchyma. As in the case of the cystic kidney the cysts tend to enlarge gradually. They contain a clear albuminous fluid and are lined by cubical epithelium. The condition is supposed to be due to some malformation of the smaller bile ducts, which fail to become connected with the main biliary tree and undergo cystic dilatation. Occasionally other congenital abnormalities such as hydrocephalus, spina bifida, and talipes may be present.

## JAUNDICE

The liver has far more important functions than the excretion of bile, but at present the estimation of those functions is a matter of great difficulty, and the study of the behavior of the bile pigments affords one of the most convenient methods for determining the state of health or disease of the liver cells. For this reason the study of jaundice or icterus is of interest to the pathologist as well as to the clinician. Jaundice is a coloration of the skin and sclerotics by bile pigment in the blood. The color varies from pale yellow to deep orange or even green. The internal organs are pigmented with the exception of the central nervous system, which usually escapes.

Bilirubin is formed from the hemoglobin of broken-down erythrocytes by the cells of the reticulo-endothelial system, principally those of the bone-marrow and spleen. If hemolysis is increased the amount of bilirubin formed will be correspondingly increased. The bile acids are synthesized only by the liver.

When the bilirubin is formed it is carried to the liver for excretion. There are three elements in a liver lobule: (1) the hepatic cell;



FIG. 269.—Swollen and detached Kupffer cells in liver sinusoids.  $\times 525$ .

(2) the bile canaliculus, which we may call the bile duct; and (3) the sinusoid, which connects the portal with the hepatic vein and is lined intermittently by Kupffer cells. (Fig. 269.) The hepatic cell is flanked on one side by the vessel, on the other side by the bile duct. The bilirubin is carried to the lobule by the blood, passes through the wall of the vessel, is excreted by the hepatic cell into the bile duct, and escapes into the intestine. In the large bowel it is reduced by bacterial action to urobilinogen which is colorless. The greater part of the urobilino-

gen is excreted in the feces, but part is absorbed into the portal circulation and passes to the liver. Part of this fraction is again excreted by the hepatic cells, but part passes on into the general circulation and is excreted in the urine. In health a very small but fairly constant amount of urobilinogen is present in the urine. When bilirubin has passed through the hepatic cells it is affected by the bile acids, possibly by direct coupling. If the altered bilirubin is then reabsorbed into the blood, as in obstructive jaundice, it is able to pass the barrier of the renal filter and appears in the urine. If it has not passed through the hepatic cells it is held up by the renal barrier and does not enter the urine, even though the amount in the blood is sufficient to produce jaundice; this is known as acholuric jaundice.

The most rational classification of jaundice is based on the relation of the bilirubin to the liver cell. The lesion responsible for the jaundice may be *before*, *in*, or *after* the bilirubin has passed through the liver cell, the result being respectively hemolytic, hepatic, or obstructive jaundice. The first two may be grouped together as retention jaundice, the liver being unable to excrete all the bilirubin, which therefore accumulates in the blood. This inability may be due to too much bilirubin being produced (hemolytic jaundice), or to sickness of the liver cells preventing them from excreting the normal amount of bilirubin (hepatic jaundice). For a further discussion of these matters and a consideration of what he calls regurgitation jaundice, Rich's excellent paper should be consulted.

1. **Obstructive Jaundice.**—The purest examples of obstructive jaundice are cases of obstruction of the common bile duct by cancer of the head of the pancreas, stone in the duct, or stricture of the duct. The pigment passes through the liver cells, but as it cannot escape, it is reabsorbed into the blood, produces clinical jaundice, and flows over into the urine. The *congenital jaundice* of children (not icterus neonatorum) due to atresia of the biliary passages belongs to this group. When the obstruction is severe little or no bile passes into the intestine, and the *stools* are *clay-colored*, because the fats remain undigested in the absence of bile. Owing to this absence no urobilinogen is formed, and as none is absorbed the urobilinogen normally present in the urine disappears completely. Quantitative estimation of the amount of urobilinogen excreted in the feces per day is of value in distinguishing between jaundice due to cancer of the head of the pancreas, an inoperable condition, and jaundice due to a stone in the common bile duct which can be removed by operation. If the jaundice is due to tumor the urobilinogen is below 5 mg. per day; if due to stone, which causes less complete obstruction, the amount is over 10 mg. (Watson). It was thought that the serum phosphatase was raised in obstructive jaundice, though not in the hemolytic and hepatic forms, but this is probably wrong.

2. **Hemolytic Jaundice.**—When there is excessive hemolysis the bilirubin carried to the liver cannot be all excreted so that some remains in the blood. This type of bilirubin cannot pass the kidney filter,

so that the jaundice is of the acholuric type although there is a great increase of urobilinogen in the urine. The jaundice is never so intense as it may become in the obstructive form. This form of jaundice is best seen in the disease known as hemolytic jaundice (also called acholuric jaundice), in which there is overactivity of the reticulo-endothelial system and increased fragility of the red blood cells, as a result of which the amount of hemolysis is considerably above normal. As might be expected, the amount of urobilinogen excreted in the feces is greatly increased.

Lesser degrees of jaundice may occur whenever there is marked hemolysis, *e. g.*, as the result of snake-bite, intraperitoneal hemorrhage, large pulmonary infarcts, ruptured tubal pregnancy, and blood infection with hemolytic streptococci. Sometimes, as in pernicious anemia, the blood bilirubin may be above normal as shown by the icterus index, but below the amount necessary to produce clinical jaundice. This is known as latent jaundice.

**3. Hepatic Jaundice.**—This form, also called toxic jaundice, is the jaundice of "hepatitis," or, more accurately, of liver necrosis. Hepato-cellular jaundice is perhaps the most descriptive term for the condition. The first effect of disease of the hepatic cells is an inability to excrete all the bilirubin, some of which therefore accumulates in the blood. An even earlier result is a retention in the blood of the urobilinogen brought from the bowel, and a corresponding increase of the urobilinogen in the urine. With continued action of the toxin the hepatic cells become more and more swollen so as to cause obstruction of the tiny bile canaliculi whose walls they form. Some of the bilirubin still passes through the sick cells, but as it cannot escape on account of the blockage of the canaliculi it is reabsorbed. If the chief effect of the lesion is retention, the bilirubin will not appear in the urine. If there is much obstruction of the canaliculi this reabsorbed bilirubin will accumulate in the blood and flow over into the urine. In the most extreme forms little or no bile may enter the intestine. In this case the stools will be clay-colored, and the urobilinogen in the urine will first diminish and finally disappear altogether.

The toxic form of jaundice covers a wide clinical range. Its most extreme manifestation is represented by acute yellow atrophy. There may be lesser degrees of toxic necrosis with recurring attacks of jaundice and a gradually developing portal cirrhosis. At the other end of the scale is the very common so-called catarrhal jaundice.

**Catarrhal Jaundice.**—This is by far the commonest form of jaundice met with clinically, but it does not fall easily and completely into any of the three great groups just described. The reason for this is that it is not a pathological entity. Clinically it is characterized by a transient attack of jaundice lasting a few days or a few weeks, which may or may not be associated with gastro-intestinal disturbances. The jaundice is usually mild, but may be so severe and continued as to arouse suspicion that it is caused by pressure on the bile duct by a cancer of the head of the pancreas.

The original view (Virchow), as the name suggests, was that the chief etiological factor was a catarrhal swelling of the opening of the common bile duct due to an acute gastro-intestinal disturbance. Later it was believed to be an extension of the inflammation into the finer ducts. The popular present-day conception of acute catarrhal jaundice is that it is a hepatitis or toxic necrosis of the liver, an acute yellow atrophy in miniature (Eppinger). There is truth in all these views, for the basis of catarrhal jaundice may be: (1) catarrhal obstruction of the opening of the bile duct, (2) toxic necrosis of the liver. Provided these lesions are transient, the jaundice will be "catarrhal" in type.

1. There may be obstruction of the opening of the common bile duct due to gastro-intestinal catarrh, as in Virchow's original case and in Eppinger's case where the patient committed suicide a week after the appearance of the jaundice. It is seldom that the pathologist is so fortunate as to get such an opportunity to examine the parts, for the condition is essentially harmless. In these cases the jaundice is obstructive in type.

2. The jaundice may be due to a mild and transient toxic necrosis of the liver, Eppinger's "acute yellow atrophy in miniature." The functional liver tests may show considerable impairment of function. Barber and Osborn report the case of a man who suffered from typical catarrhal jaundice for a week, and died at the end of that time of a fractured skull. The essential lesion was in the liver cells, which showed numerous mitoses (an indication that necrosis had occurred) and contained granules of bile pigment.

**Infectious Jaundice.**—It sometimes happens that epidemics of jaundice break out amongst large groups of men living together, as under active service conditions. As no bacterial agent has been isolated from these cases it has been suggested that the outbreak is due to a virus infection. During World War II similar outbreaks appeared as the result of injections of certain batches of convalescent serum (measles, mumps) and yellow-fever vaccine containing serum. These cases of so-called serum jaundice are apparently due to an *infectious hepatitis* and have been attributed to a virus. A remarkable feature in these cases is the long interval, from sixty to one hundred days, between injection of the icterogenic agent and the development of jaundice. The infective agent has been shown to be excreted in the feces, and it is believed that it is transmitted by drinking water (Neefe and Stokes).

**Symptoms of Jaundice.**—The principal symptoms are due to a retention of bile salts rather than to the bile pigment. In the disease known as hemolytic jaundice where the liver cells are normal there is no retention of bile salts, so that there are none of the characteristic symptoms. Such a dissociation between bile salts and bile pigment is spoken of as dissociated jaundice. In obstructive jaundice the salts as well as the pigment are retained, and the patient suffers from severe and sometimes uncontrollable itching, bradycardia (slow pulse), hemorrhage due to injury of the capillary endothelium by the bile salts, and various nervous symptoms. The blood cholesterol, which should normally escape in the bile, is increased, and there may be deposits of



cholesterol in the skin which form small yellow nodules known as xanthomata. Bleeding is an important feature of jaundice, and postoperative bleeding may prove fatal. It is due to a marked fall in the plasma prothrombin, associated with prolonged clotting time. The low prothrombin level is due to: (1) failure of absorption of vitamin K from the intestine owing to absence of bile; (2) damage to the liver, in which organ prothrombin is formed from vitamin K. Administration of synthetic vitamin K before operation will bring the prothrombin level back to normal and prevent hemorrhage. In catarrhal jaundice there is a characteristic leucopenia or diminution in the white cells of the blood, which often fall to 4000 per c.mm. and sometimes even to 2000. The chief decrease is in the polymorphonuclears.

**Icterus Neonatorum.**—Some degree of jaundice is very common in the newly-born. This is merely an exaggeration of a physiological condition present in all infants after birth. The jaundice is therefore hemolytic in type, and may remain latent or become visible. The reason for the hemolysis is that the child at birth has a polycythemia, an excessive number of red blood cells, because *in utero* it has been living in a condition of anoxemia or constant lack of oxygen. After birth the need for the polycythemia ceases, the excess red cells are destroyed by hemolysis, an increased amount of bilirubin is produced, and there is jaundice either latent or clinical.

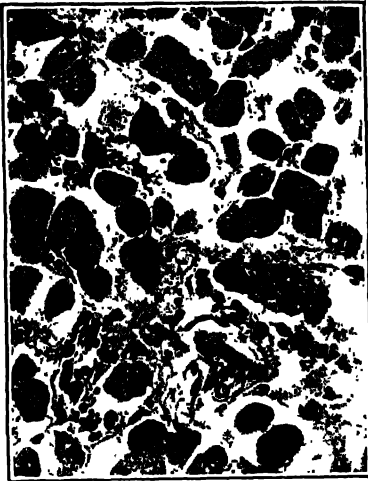


FIG. 270.—Dissociation of liver cells in Weil's disease.  $\times 300$ .



FIG. 271.—Spirochete in kidney in Weil's disease.  $\times 1350$ .

**Weil's Disease. Spirochaetosis Icterohaemorrhagica.**—Weil's disease is a very acute epidemic infection, characterized by marked jaundice, hemorrhages from the mucous membranes, fever, enlargement of the spleen and nephritis. There is marked evidence of blood destruction, and blood and bile appear in the urine. The disease is caused by a specific spirochete (*Spirochaeta icterohaemorrhagiae*). It occurs in troops on active service, and workers in mines, sewers and abattoirs. The factors common to these occupations are dampness of the soil and close association with rats.

The rat seems to act as a reservoir of infection, excreting great numbers of spirochetes in the urine. The spirochetes may penetrate the skin directly. Fleas may act as an intermediate host. A few cases have been caused by rat bites. There is also a canine form, caused by *S. canicola*, in which the

infection is rarely conveyed from the dog to man. The disease usually lasts about three weeks. During the first week the spirochetes are present in the blood. In the second week they disappear from the blood, but appear in the urine.

In addition to cloudy swelling the liver may show small areas of focal necrosis, in which mitoses or amitotic division can be seen. Even more striking than mitoses is the presence of binucleated liver cells, as if amitotic division of the nucleus had occurred. In some cases there is a striking dissociation of liver cells, the columns being broken up and the cells separated from one another. (Fig. 270.) The renal tubules show degeneration or actual necrosis. There are degenerative changes in the muscle fibers, especially in the legs, and focal ischemic necrosis in the brain. The spirochetes, which often present a terminal hook like a shepherd's crook (Fig. 271), lack the sharp spirals of the spirochete of syphilis. They are present in large numbers in the liver, kidney and adrenal, and in smaller numbers in other organs. If a guinea-pig is inoculated with blood during the first week or with urine during the second week it will develop the disease and will show hemorrhages in the lungs and enormous numbers of spirochetes in the liver and kidney. Some strains, however, are not pathogenic for guinea-pigs. The patient's urine may also be examined directly for spirochetes by the dark-field method. Immune bodies are developed in the blood, so that an agglutination test is of value for diagnosis.

## THE GALL-BLADDER

The normal gall-bladder is 3 to 4 inches long, and its capacity is about 45 cc. The liver produces nearly a liter of bile a day, but only some of this reaches the duodenum. The rest is absorbed, or rather the watery part is absorbed, by the wall of the gall-bladder, so that the bile is greatly concentrated, it may be as much as 10 times. The inner surface of the gall-bladder appears to be designed for absorption. The entire surface is divided into a series of polygonal spaces by delicate walls of mucous membrane, which are best appreciated if the gall-bladder is examined under water by means of a magnifying glass or a binocular dissecting microscope. When this is done the transparent mucous folds, gossamer-like in delicacy, are seen to float up like the leaves of a water plant in a clear pool. The Graham visualization test depends on the power of the gall-bladder to concentrate a dye (tetraiodophenolphthalein), which is excreted by the liver after being administered, passes into the gall-bladder, and is there concentrated sufficiently to make the outline visible in a roentgen-ray picture. Loss of the concentrating power due to disease of the wall gives a negative test, and is apparently an early result of gall-bladder disease.

The effect of the introduction into the duodenum of magnesium sulphate and many other substances, even water, is to excite a flow of bile from the biliary passages in the liver. It is unlikely, as was at one time supposed, that any real emptying of the gall-bladder is produced in this way. The gall-bladder can, however, be made to empty by giving a "fat" meal consisting of egg-yolk and cream (Boyden). During pregnancy this normal emptying does not occur, at least in the experimental animal (Mann and Higgins). The interference appears to be chemical rather than mechanical. When the uterus is emptied the normal response to the administration of fat returns. These observations suggest that part of the relationship of gall stones to pregnancy depends on the production of stasis.

A peculiar feature of the gall-bladder, pointed out by McKibbin and McDonald, is that polymorphonuclear leucocytes are frequently present in one or more layers of the organ without any other evidence of inflammation. These cells are also present in the dog's gall-bladder. They do not indicate inflammation, and appear to be metabolic in function.

The efferent lymphatics of the gall-bladder drain into the cystic lymph gland, situated at the junction of the neck of the gall-bladder and the cystic duct.

When the gall-bladder is infected bacteria may be found in this gland (see below). The gall-bladder has a double nerve supply, partly cerebrospinal from the vagus, partly sympathetic from the ninth dorsal segment of the cord. The stomach has the same nerve supply, so that reflex gastric symptoms are a common result of gall-bladder disease.

The muscle coat ceases abruptly at the neck of the gall-bladder, and the bile ducts (cystic and common) are fibro-elastic tubes with only a few isolated muscle fibers. There is an abundance of nerve fibers in the outer part of the wall of the ducts. From these facts it is evident that biliary colic is due to distention of the duct and not to muscular spasm.

### CHOLECYSTITIS

**Etiology.**—The two possible factors responsible for the production of cholecystitis or inflammation of the gall-bladder are bacteria and the chemical irritation of retained bile. The bacteriology is mixed, the principal organisms found being *B. coli* and *Streptococci* (Williams and McLachlan, Magner and Hutcheson). Cultures of apparently normal gall-bladders not infrequently show similar bacteria derived from the liver. The acutely inflamed appendix contains enormous numbers of organisms, but the acutely inflamed gall-bladder may contain few or none. From these facts it is evident that whilst in some cases bacterial infection may be the chief causal factor, in others some non-bacterial irritant must be looked for.

Occlusion of the cystic duct is probably the most important single factor in the production of acute cholecystitis (Andrews). The lumen of the duct is small, and its wall is thick and deeply pocketed with sinuses, so that a slight degree of inflammation will cause narrowing or closure of the duct. Calculi causing obstruction may be associated either with acute or chronic inflammation. The intensity of the ensuing inflammation depends on the composition of the imprisoned bile (Womack and Bricker). When the cystic duct is tied after the gall-bladder has been emptied and washed with saline, no inflammation develops. When the gall-bladder contains bile there is edema, round-cell infiltration and fibrosis. When the bile is replaced by a solution of dried bile double the concentration of that of normal bile, the wall undergoes complete necrosis, although when the cystic duct is open the changes are slight and transient. It is reasonable to suggest that in chronic as well as in acute cholecystitis the chemical factor is of great importance. This would serve to explain the extreme diffuseness of the lesions so different from the patchy focal lesions of chronic inflammation in other organs, and also the association of cholecystitis with gall stones which are an important cause of biliary obstruction.

**Acute Cholecystitis.**—The wall of the gall-bladder is thickened, the serous surface is congested and covered by a fibrinous exudate, and the mucosa is bright red or purple. When obstruction of the cystic duct is complete the lumen is distended with what appears to be purulent fluid, so that the condition is known as *empyema of the gall-bladder*. This is often not a true empyema, for the "purulent" fluid is frequently found to consist of an emulsion of cholesterol crystals. *Microscopically*

the most striking picture is a marked inflammatory edema, which is responsible for most of the thickening. Polymorphonuclears are relatively few in number in striking contrast to the abundant purulent exudate in acute appendicitis, suggesting a non-bacterial inflammation. Reference has already been made to the presence of polymorphonuclear leucocytes in the uninflamed gall-bladder. In some cases the picture is that of an ordinary purulent inflammation, and in these the bacterial count in the bile is enormously increased.

**Chronic Cholecystitis.**—Chronic cholecystitis may be the result of an acute attack, but usually it is chronic from the outset and the symptoms develop gradually and insidiously. There is a low-grade inflammatory reaction commencing in the outer part of the wall and



FIG. 272.—Chronic cholecystitis. The gall-bladder is dilated, its wall moderately thickened, the fundus contains a large calculus, and the lining shows reticulation.

gradually spreading throughout the gall-bladder. The gross appearance varies considerably. The bluish color of the thin-walled normal gall-bladder is lost, and the surface may be opaque; it is sometimes yellow owing to an accumulation of subserous fat. The wall is thickened and fibrosed (Fig. 272), and the cavity may be of normal size, dilated or contracted. If there has been no obstruction at the neck of the gall-bladder, the cavity is likely to be small from contraction of the new fibrous tissue. Sometimes the gall-bladder is contracted upon one or two large stones, so that no room is left for any bile. Should obstruction be present owing to inflammatory swelling, cicatricial contraction, or the impaction of a stone at the neck of the bladder, there will be dilatation of the cavity as well as thickening of the wall. If obstruction

becomes marked before the inflammatory changes have had time to cause thickening, the wall of the greatly dilated bladder may be quite thin. The cavity is filled with clear, colorless, watery fluid secreted by the lining epithelial cells, a condition known as *hydrops* of the gall-bladder. The bile pigment is absorbed, and no more can enter owing to the obstruction. The condition of the gall-bladder depends on the balance between infection and obstruction. In the milder cases the surgeon may have great difficulty in deciding at operation whether or not the gall-bladder is diseased and should be removed. The cystic gland at the neck of the gall-bladder is usually enlarged.

When the gall-bladder is opened the appearance again varies. The

color is usually not much changed, but it may be a deep red. With a hand lens or the dissecting microscope the thin folds of the normal mucosa are seen to be thick and swollen, but when the organ is markedly distended as in hydrops they may disappear completely. It is evident that the absorbing and concentrating power of the gall-bladder will be greatly impaired or lost, so that no shadow is seen with Graham's visualization test. The surface may be eroded by the pressure of calculi, but it is remarkable how intact the surface epithelium usually is even in the worst-looking gall-bladders. As a result of contraction of the fibrous tissue the surface may become reticulated and scarred, so as to present an interlacing network of fine bands which show through the atrophic mucosa with great distinctness.

The *microscopic appearance* is one of chronic inflammation usually involving the entire organ. There are definite groups of lymphocytes, and occasionally large numbers of plasma cells and eosinophils, as well as a more diffuse infiltration. Single sec-



FIG. 273.—Chronic cholecystitis. The wall is greatly thickened and groups of inflammatory cells are scattered through it. The muscle is largely replaced by fibrous tissue.  $\times 40$ .

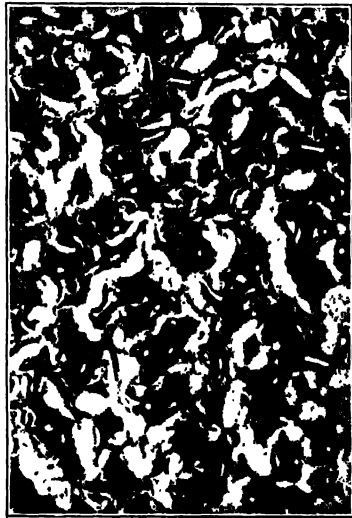


FIG. 274.—Cholesterosis of the gall-bladder under the dissecting microscope. The ridges of mucosa are loaded with lipid.

tions are of doubtful value, for serial sections show a high degree of patchiness of infiltration, which is often more marked on the hepatic than on the peritoneal surface. The folds of mucosa are thickened owing to edema. It must be remembered that the normal mucosa contains large numbers of round cells; these must not be mistaken

for an inflammatory infiltration. The epithelium is usually intact in well-fixed tissue. Postmortem material is useless as, immediately after death, the bile digests away the epithelial lining in both the normal and pathological gall-bladder. The same is true, though in a lesser degree, of gall-bladders removed at operation unless they are at once opened and placed in formalin. The very best results are obtained by distending with formalin the freshly removed and emptied gall-bladder. In the later stages there is an abundant formation of granulation tissue which causes great thickening of the wall (Fig. 273), and is ultimately replaced by fibrous tissue, so that the gall-bladder is converted into an inert bag incapable of contraction.



FIG. 275.—Cholesterolosis of the gall-bladder. There are large masses of cholesterol in the mucosa and also in the deeper parts of the wall. A pedunculated mass is almost separated from its attachment. (From Boyd's Surgical Pathology.)

**Cholesterolosis of the Gall-bladder.**—This is also known as the *lipoid gall-bladder* and the *strawberry gall-bladder*. The wall is usually a little thickened, but the most striking change is in the mucosa, over the surface of which are scattered little yellow flecks like the seeds of a strawberry. The condition is best seen with the hand lens or under the dissecting microscope, which gives a much better idea of the lesion than a microscopic section. (Fig. 274.) The normal delicate mucosal folds are seen to be loaded down by opaque yellow masses which first appear on the summit of the ridges. These are deposits of cholesterol ester which can be studied in frozen sections stained with a fat stain (Scharlach, osmic acid), or under crossed Nicol's prisms where their anisotropic character is revealed. The lipid is found at the base of the epithelial cells of the mucosa and in phagocytic histiocytes in the

## PLATE XIV



**Polypoid Mass of Cholesterol Ready to Separate.**

Early case of strawberry gall-bladder. Stained with Scharrlach R.

*(Boyl's Surgical Pathology, courtesy of W. B. Saunders Company.)*





deeper part of the wall. A mass of lipoid in the mucosa may become pedunculated and is then readily detached, when it may act as the nucleus around which a gall stone may be formed. (Fig. 275 and Plate XIV.)

The explanation of the condition is not easy. Cholesterol seems to be absorbed by the gall-bladder mucosa, although Elman and Graham believe that it is excreted, and that the excretion is increased by inflammation. In the condition of cholesterolosis there is storage of cholesterol under the mucosa. Two etiological factors are probably at work. The first and most important is a disturbance of cholesterol metabolism, as a result of which the amount of cholesterol in the blood and bile is increased. The second is a mild degree of chronic inflammation. It is probable that the condition of cholesterolosis is not necessarily a permanent one, and that most if not all the cholesterol may finally disappear. There is no convincing evidence that these deposits can cause symptoms or that they are of any clinical significance.

**Stasis Gall-bladder.** — Westphal and other continental writers have pointed out that the entire extra-hepatic biliary tract may be regarded as a physiological unit whose neuromuscular mechanism can be disturbed reflexly. This disturbance may cause gall-bladder symptoms even amounting to colic without inflammation and without stones. The effect on the gall-bladder is the production of stasis. There may be *hypertonic stasis*, with a thick-walled muscular gall-bladder, dilatation of the common duct, and hypertrophy of the upper or duodenal part of the sphincter of Oddi; this is caused by overactivity of the vagus. Or there may be *hypotonic stasis*, with a distended thin-walled gall-bladder, normal common duct, and poorly developed duodenal sphincter; this is caused by overactivity of the sympathetic, stimulation of which leads to relaxation of the gall-bladder.

**Cholecystitis Glandularis.** — Sometimes, apparently as the result of chronic irritation, the epithelium lining the gall-bladder commences to proliferate and form gland-like spaces. This proliferation may take the form of a papillary projection, commonly called papilloma of the gall-bladder. In other cases the growth is into the depth of the wall and new glands are formed which may penetrate the entire thickness of the wall and form a mass on the serous surface (Fig. 276). An apparent diverticulum or pocket may thus be formed, and its



FIG. 276.—Formation of new glands in whole thickness of gall-bladder wall.

communication with the lumen of the gall-bladder may or may not be apparent. These various appearances are merely an exaggeration of the structures known variously as Luschka's crypts and Rokitansky-Aschoff sinuses, which Robertson and Ferguson point out are merely diverticula of the gall-bladder, similar to the diverticula occurring in the colon and urinary bladder. They are protrusions of the mucosa through the muscular coat, invaginations which are found in about half of all gall-bladders removed in persons over thirty years of age.

### GALL STONES

Gall stones or biliary calculi are usually formed in the gall-bladder, but may be formed in the bile passages, especially those within the liver. They may be single or multiple; sometimes there are several hundred small stones. There are three constituents, cholesterol, bilirubin, and calcium. As the proportion of these varies, so do the calculi vary in their gross appearance. Three main varieties may be recognized: (1) the pure cholesterol stone, (2) the pure pigment stone, and (3) the common infective or mixed stone.

**Etiology.**—The etiology of gall stones is still unsettled. We are certainly powerless to prevent their formation. Three factors must play a part: infection, stasis, and high bile cholesterol. It does not follow that all three need be present in any given case. (1) *Infection*. This is the principal factor. All the infective or mixed stones are associated with cholecystitis. The cholecystitis causes the calculi, not *vice versa*. Cholesterol is held in solution in the bile in a series of loose chemical complexes with bile salts. These may easily be broken up, *e. g.*, by dialysis. When the bile salts are removed the cholesterol is precipitated. There is no differential absorption of cholesterol and bile salts by the normal gall-bladder. The infected gall-bladder, on the other hand, absorbs bile salts rapidly but cholesterol very slowly, so that the latter tends to be precipitated. Fatty acids in the bile are even more effective than bile salts in keeping cholesterol in solution. This may explain the rarity of gall stones in the dog and sheep, who have a high fatty acid content in bile, and the high incidence in man, who has a low fatty acid content. When a nucleus of cholesterol is established bilirubin is laid down around it to form a mixed stone. There is a general impression that typhoid fever, in which the bacilli always lodge in the gall-bladder, is especially associated with calculus formation. (2) *Stasis* probably plays a part. The fact that in pregnancy the gall-bladder does not empty in response to a fat meal has already been referred to. Gall stones are much commoner in women (3 or 4 to 1), especially in those who have borne children. Patients with gall stones are often "fat, female, and forty." (3) *High bile cholesterol*, associated in turn with high blood cholesterol, is a possible factor, although the hypercholesterolemia may have disappeared by the time symptoms have begun to manifest themselves. The blood cholesterol is high in pregnancy and typhoid fever. Deposits of cholesterol in the mucosa may become pedunculated, detached, and form the starting-point of calculi.

**Pure Cholesterol Stone.**—This is also called the *metabolic stone*, because it is essentially due to a disturbance of cholesterol metabolism. It is large, oval, white, usually single, of light weight, and the cut surface shows a characteristic radiate structure and glistening crystals of cholesterol. The factors which favor its formation are high bile cholesterol and stasis in the gall-bladder. It is a silent stone and usually causes no symptoms. There is no change in the gross appearance of the gall-bladder. The stone may become impacted in the neck of the gall-bladder and lead to a condition of hydrops. Sometimes the impaction is followed by infection. Should the stone now roll back into the gall-bladder and allow bile to enter, bilirubin calcium is deposited on the surface and a *combination stone* is formed.

**Pure Pigment Stone.**—These stones are multiple, very small, black in color, friable, and consist of bilirubin. They contain no cholesterol. They are often present in hemolytic jaundice, but are not confined to that condition. Like the previous stone they appear to be metabolic in origin. When very small and numerous they constitute biliary gravel.

**Infective or Mixed Stones.**—This is the common variety, composed of cholesterol, bilirubin, and calcium. The pigment and cholesterol are laid down in alternate layers, so that the cut surface presents a concentric arrangement of laminae. The general color is yellow or brown, and the stones are faceted and polished unless there is only one. (Fig. 277.) There may be two or three families of stones, all the members of each family being about the same size and probably starting life at the same time. In the center there is usually a nucleus of mucus and cellular debris, and if the crystalline material is dissolved out by chloroform a protein frame work of concentric laminae is left, indicating that these stones are formed in inflammatory medium rich in protein and therefore deserve to be called infective.

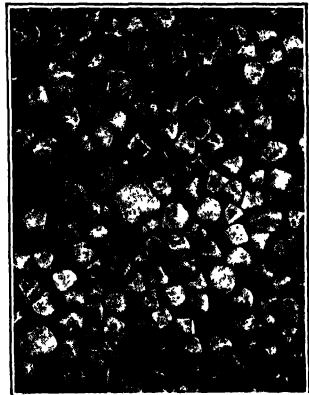


FIG. 277.—Infective gall stones. The faceted stones are very uniform in size.

The effect on the gall-bladder varies with the kind of stone, for the changes are due to inflammation. The metabolic stones (cholesterol and pigment) are likely to be associated with a gall-bladder which appears normal unless the stone causes obstruction. The infective stone is associated with cholecystitis, so that the wall will be thickened and the lumen usually contracted, but dilated if impaction has occurred early. (Fig. 278.) Stone in the common duct is seldom associated with dilatation (see below). The pressure of a stone may produce ulceration so that a deep pocket is formed. This may perforate the

wall, and the stone escapes into the peritoneal cavity or into a cavity walled off by adhesions. If the gall-bladder becomes adherent to the bowel the stone may perforate into the transverse colon or into the ileum.



FIG. 278.—Facetted calculi in gall-bladder with moderately thickened wall.

**The Relation of Symptoms to Lesions.**—Cholecystitis and calculi will be considered together. In *acute cholecystitis* the severe pain and tenderness over the gall-bladder are explained by the acute inflammatory swelling and tension of the wall. The patient will have general symptoms of septic infection (fever, leucocytosis, etc.). There may be some jaundice owing to spread of the inflammation to the common bile duct with obstruction. *Biliary colic* is due to the passage of a small stone along the cystic and common bile ducts, causing distention of these passages. There is probably no spasm owing to the absence of muscle fibers. Colic is not a certain proof of a stone, for the passage of masses of pus or mucus may also produce colic. The mere presence of stones in the gall-bladder may or may not be associated with symptoms. Stones are often found at postmortem when the patient had no symptoms to suggest gall-bladder disease. When symptoms do occur, they are due to the associated cholecystitis. The metabolic pure cholesterol stone is silent.

The symptoms of *chronic cholecystitis* are for the most part referable to the stomach, *i. e.*, dyspepsia, nausea, belching of gas, and a feeling of fulness and bloating. These symptoms are aggravated by fatty foods. It will be remembered that food containing much fat causes the gall-bladder to contract and empty itself, and if the wall is inflamed this may cause discomfort. The stomach suffers because it has the same double nerve supply (vagus and sympathetic from the ninth dorsal segment) as the gall-bladder, and appears to be a specially sensitive and, as it were, sympathizing organ. The inflammation is most marked in the outer part of the gall-bladder wall, so that the nerve endings are irritated. Irritation of the vagal nerve endings tends to be reflected to the stomach and to cause hyperchlorhydria and regurgitation. When the inflammation is more severe the sensory stimulus is greater, passing up the sympathetic to the ninth dorsal segment and then down to the stomach, where it causes pylorospasm and gastric discomfort, as the sympathetic is the motor nerve to the pyloric sphincter.

It seems improbable that *cholesterolosis* of the gall-bladder can of itself give rise to symptoms. The condition is not infrequently found at autopsy in persons who have never had any symptoms of gall-bladder disease.

### OBSTRUCTION OF THE BILIARY PASSAGES

The biliary passages may be obstructed in different ways and at different levels. The effect on the biliary passages varies with these differences. *Courvoisier's law*, now nearly a hundred years old, states that in jaundice due to pressure on the common bile duct from without, as by cancer of the head of the pancreas, the gall-bladder is greatly distended, while in jaundice due to impaction of a stone in the common duct the gall-bladder is not distended to such an extent that it can be detected clinically. This is a useful working rule which still holds good. The reason is that in obstruction due to stone there is already a cholecystitis, the wall of the gall-bladder is thickened, so that it cannot be greatly distended; indeed it may be considerably contracted. It is important to remember that many stones may be lodged in the common duct; I have seen as many as 25 in one case, the gall-bladder containing 23 more.

The site of the obstruction has an influence on the contents of the dilated ducts. (1) If the obstruction is in the common duct (the usual site) the biliary passages are still in free communication with the gall-bladder, which concentrates the bile retained in the passages so that it becomes thick and dark. (2) If the obstruction is above the entrance of the cystic duct this concentrating mechanism can no longer operate, the bilirubin is absorbed, and the epithelial cells lining the hepatic ducts secrete a clear watery fluid, the so-called *white bile*, which fills and distends the biliary passages. It is evident that this fluid is not bile at all. If the wall of the gall-bladder is degraded by disease so that it loses its concentrating power, an obstruction in the common duct will produce the same effect as if it was above the entrance of the cystic duct, and the entire biliary tract, including the gall-bladder, will become filled with "white bile." (3) If the cystic duct is blocked by an impacted calculus or a tumor, the bile in the isolated gall-bladder is first absorbed, and is then replaced by clear fluid secreted by the



FIG. 279.—Thick secretion of mucus in gall-bladder with obstructed cystic duct. X 85.

lining epithelium. This fluid is much more mucoid than that secreted by the lining of the hepatic ducts, and the condition is called *mucocele* or *hydrops* of the gall-bladder. (Fig. 279.)

### CARCINOMA OF THE GALL-BLADDER

Cancer of the gall-bladder is a relatively common condition. This is not surprising when it is recalled that derivatives of cholic acid are amongst the most powerful of the chemical carcinogens. It bears a close relationship to the presence of gall stones, so that the disease is four or five times commoner in women than in men. It thus offers a striking exception to the general rule that cancer of the digestive tract is much more common in the male sex.



FIG. 280.—Papillary carcinoma at neck of gall-bladder.

The usual sites are the fundus and the neck of the gall-bladder. It takes an infiltrating form, causing great thickening of the wall, but sometimes there is a large soft papillomatous mass which projects into the cavity of the organ. (Fig. 280.) *Microscopically* the structure is that of an adenocarcinoma, but in rare cases it may be that of an epidermoid carcinoma, owing to metaplasia of the columnar into squamous-cell epithelium from the chronic irritation which precedes the development of the tumor. The liver is invaded early, and jaundice is a constant symptom.

*Carcinoma of the bile ducts* usually grows at the lower end of the common duct, where it forms a small, hard, white mass readily mistaken

for an impacted calculus. It is a rather rare condition, and is usually adenocarcinomatous in structure.

**Liver Death.**—It sometimes happens that cholecystectomy, operations on the bile ducts, or traumatic injury to the liver, is followed after a latent interval by sudden and extreme hyperpyrexia ending in death. These cases may be divided into two groups; in the first hyperpyrexia develops in twenty-four to forty-eight hours, and the only lesion is degeneration (sometimes necrosis) of the liver cells; in the second the symptoms do not develop for four to five days, the clinical picture is one of renal failure and uremia, and there are marked degenerative changes in the kidneys as well as the liver. In both groups death is too late for shock, and there is no sign of infection at autopsy. Boyce and McFetridge have reproduced the syndrome in rabbits by first obstructing the biliary tree and then suddenly releasing the obstruction, and also by producing subcapsular trauma to the liver. They suggest that sudden death with hyperpyrexia and what may be called the *hepatorenal syndrome* are successive stages of the same pathological process. It may be that the liver is damaged to some degree in biliary tract disease and its detoxifying power interfered with. The various injurious factors inseparable from an abdominal operation and the sudden release of obstruction may intensify this damage, as a result of which the circulation is flooded with toxins, some of which may be due to direct damage to liver tissue. These toxins, when not powerful enough to produce early death, may injure the renal epithelium and cause death from renal failure.

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## CHAPTER XXII

### THE PANCREAS

THE pancreas is in reality a double organ. It is an acinar digestive gland secreting the most powerful of all the digestive juices. For this reason postmortem changes occur very quickly, and the finer forms of investigation, such as an examination of the islet tissue for the specific A and B granules, should be carried out as soon after death as possible. It is also one of the endocrine glands, for the islets of Langerhans form one of the chief regulators of carbohydrate metabolism. The pathology of the pancreas therefore assumes a twofold aspect.

#### PANCREATITIS

**Acute Hemorrhagic Pancreatitis.**—This is really a pancreatic necrosis to which hemorrhage may or may not be added. A preferable name would therefore be *acute pancreatic necrosis*. This is one of the acute abdominal catastrophes. The pain comes on suddenly, after a large meal, and is even more agonizing than that of perforated gastric ulcer. The patient lies perfectly motionless, not tossing about as in renal or biliary colic, passes into a condition of shock, and shows a peculiar and characteristic slaty-blue cyanosis. There is marked increase in the serum amylase.

**Etiology.**—The cause of the condition is a matter of perennial dispute. The acute necrosis is due to the action of the pancreatic enzymes liberated from the ducts. The problem is to explain how they escape. The usual view is that it is due to the passage of infected bile along the pancreatic duct; this activates the trypsinogen in the pancreas and converts it into trypsin, which proceeds to digest the pancreas. More than one-half the cases are associated with cholecystitis or calculi. Opie originally pointed out that if the common bile duct and pancreatic duct open into a common chamber (as occurs in 70 per cent of persons), impaction of a calculus at the ampulla of Vater will cause the bile to flow into the pancreas. This is a possible but very uncommon cause. Archibald has shown that in the cat spasm of the muscle of Oddi at the ampulla of Vater is followed by a flow of bile into the pancreas, and such spasm may be produced by pressure on the gall-bladder or by painting the ampulla with weak hydrochloric acid. This is a probable cause in many cases. The matter cannot be regarded as settled, for Mann has pointed out that in the human subject the sphincter is usually not placed distal to the entry of both ducts, but proximal to the termination of the bile duct, and he suggests that here clinical imagination has preceded the demonstrated facts.

Rich and Duff have suggested a different explanation. They found that in both human and experimental hemorrhagic pancreatitis the constant and specific lesion was rapid necrosis of the walls of the arteries and veins, hemorrhage being due to rupture of the necrotic walls. Moreover, they found that the pancreatic juice was able to produce necrosis without activation of the trypsinogen by intestinal contents or bile. They believe that the mechanism involved is rupture of dilated thinned-out acini behind an obstructed duct, this rupture being liable to occur from increased pressure in the ducts due to marked secretion after a large meal. The main duct may be obstructed by a gall stone at the ampulla, but they found that the obstruction was usually in one of the smaller branches, being caused by squamous metaplasia and piling up of the lining epithelium. This lesion was present in over half the cases of hemorrhagic pancreatitis. The probable truth is that all of the factors outlined above may at times be responsible for producing the condition.

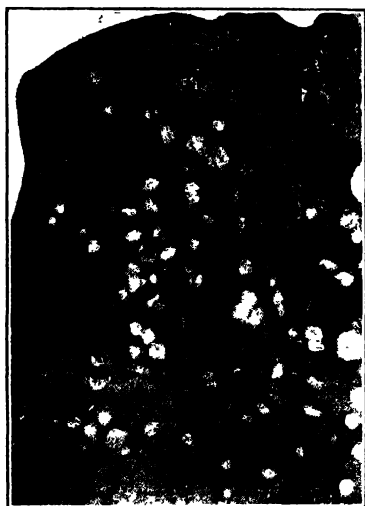


FIG. 281.—Fat necrosis of pancreas.

The *cause of death* is probably the poisonous split-protein products formed as the result of partial digestion of the pancreatic tissue. These products are absorbed very quickly, and this, together with the profound degree of shock, perhaps accounts for the extraordinarily rapid termination of many of the cases.

**Lesions.**—The pancreas is swollen, soft, and dark in color. It may be red from hemorrhage or black and gangrenous. Hemorrhage is an accidental occurrence, which may or may not be present. Sometimes it dominates the picture. A pancreas may appear normal to the naked eye and yet may show the characteristic necrosis microscopically. The marked swelling is probably responsible for much of the severe pain. Small

necrotic areas may be replaced by fibrous tissue. Larger areas may be infected and form abscesses. The greater part of the pancreas may be destroyed. The peritoneal cavity contains a characteristic fluid, dirty, fatty, and beef-juice in appearance. The *microscopic appearance* is one of great necrosis of the acinar tissue, so that in the advanced cases no structure can be made out. A varying degree of hemorrhage takes place into this necrotic tissue.

*Fat necrosis* is often seen in acute pancreatitis and is pathognomonic of that condition when encountered at operation. Small, dull, opaque white areas are scattered over the surface of the pancreas and the surrounding omentum and mesentery. (Fig. 281.) These represent

areas of fat which have been broken down by the lipase in the liberated pancreatic juice. Glycerol and fatty acids are formed; the glycerol is absorbed, and the fatty acids are deposited in the cell as acicular crystals. The areas tend to be absorbed in the course of a few weeks, but the fatty acids may unite with calcium, so that some of the patches may become calcified. *Microscopically* the necrosed cells have an opaque appearance, in comparison with the clear cells of normal fat which is all dissolved out by the chloroform or oxydol used for clearing the tissue. One part of a fat globule may show this opaque appearance while the rest of it is clear. (Fig. 17, page 52.) The necrotic area is usually surrounded by a zone of leucocytes.

**Chronic Pancreatitis.**—In this condition the pancreas is hard and sclerotic, and there is marked atrophy of the parenchyma and increase of the fibrous stroma. The most probable cause is the repeated entry of mildly infected bile into the pancreatic duct, but of this it is impossible to be certain. As the islets of Langerhans do not belong to the acinar system they are usually spared, but if the sclerosis is severe the islets are injured, and diabetes is then present. On account of the hardness the condition is easily mistaken by the surgeon for carcinoma of the head of the pancreas.

## DIABETES MELLITUS

**Etiology.**—The cause of diabetes is unknown. The disease usually begins after middle life, but is more severe in the young. Obesity seems to be a predisposing factor. The essence of the condition appears to be a disturbance of the normal balance of the factors regulating carbohydrate metabolism. In this regulation the liver plays the most important part, but the hormonal output of the pancreas, pituitary and adrenals are also essential. In all cases of diabetes there is an insufficiency of insulin in relation to the needs of the organism, but the actual secretion may be normal or increased. In other words, it is not necessarily a disease of the pancreas. In one of my cases not only were the islets apparently normal, but there was also an adenoma of the islets. The pituitary, thyroid and adrenals have an action antagonistic to that of the pancreas.

Excision of the pituitary relieves the experimental diabetes produced by removal of the pancreas (Houssay). Conversely it has been shown that permanent diabetes can be caused by repeated injections of extract of the anterior pituitary (Young), perhaps due to initial stimulation and subsequent exhaustion of the islets. In the early stages there is disappearance of the granules in the Beta cells, hydropic degeneration of these cells, and marked cellular proliferation as indicated by numerous mitoses. The later changes are hyalinization with final complete disappearance of the islets. Similar exhaustive changes are seen in experimental diabetes produced by excision of nine-tenths of the pancreas followed by a carbohydrate diet. In the remaining portion of the pancreas the exhausted Beta cells show loss of the specific granules and marked hydropic degeneration (Fig. 282); finally they rupture or degenerate and disappear.

Selective necrosis of the islets can be produced by the intravenous injection of alloxan, one of the components of uric acid (Shaw and Dunn). There is complete necrosis of the islet tissue although the acinar cells are unaffected. The *alloxan* diabetes which results is characterized by a marked and fatal hypoglycemia, which is preceded by a puzzling transient hyperglycemia. There are thus three ways of producing diabetes experimentally: (1) by pancreatectomy, (2) by injection of anterior pituitary extract, (3) by injection of alloxan.



FIG. 282.—Islet of Langerhans in experimental diabetes showing extreme hydropic degeneration of the Beta cells.  $\times 500$ . (From a preparation by Dr. D. J. Bowie.)

**Symptoms.**—Glycosuria is the chief symptom of diabetes (*mellitus*, sweetened with honey), associated with polyuria (*diabetes*, a syphon or running through), excessive thirst and hunger, and marked loss of weight. Another group of symptoms due to incomplete combustion of fats are manifestations of acidosis, *e. g.*, air hunger, coma, ketone bodies in the urine, and lipemia. Pruritus, carotinemia, gall stones, arteriosclerosis, and gangrene of the extremities may occur.

**Lesions.**—Although the patient may have died of diabetes, the pancreas generally appears normal to the naked eye, because the acinar tissue is unaffected. The microscopic appearance is usually disappointing. The islets are often greatly diminished in number, but they may appear to be normally abundant. Indeed in some cases they may be hypertrophied. With ordinary technic they may seem to be healthy, but if the autopsy is performed within an hour after death and the tissue is fixed in Zenker's solution to prevent shrinkage it may be possible to detect hydropic degeneration. Disappearance of the granules in the Beta cells is a basic lesion, but one which it is very difficult to demonstrate, as the technic demands special fixatives, special stains and very fresh tissue.

In human diabetes it is seldom possible to demonstrate the lesions seen in the experimental animal. For one thing, the material is seldom sufficiently fresh. Moreover many diabetics do not die of diabetes, but of arteriosclerosis, gangrene, etc. In such patients the islets

PLATE XV



Glycogen in Renal Tubules

From a case of diabetes mellitus. Stained with Best's carmine.



are no longer under strain. They may, indeed, have undergone regeneration. In death from diabetic coma there is much greater chance of finding hydropic cells. Hyaline degeneration of the islets is often seen (Fig. 283), but it is also common in persons over middle age, *i. e.*, the diabetic period. Finally it must be remembered that diabetes is the result of a disturbance of the normal balance of the factors regulating carbohydrate metabolism, and that in some cases the pancreas may not be the chief offender.

*Changes in other organs* may occur. In the kidney there may be two characteristic changes. The first is the presence of large amounts of *glycogen in the renal tubules*, giving the cells a characteristic clear transparent appearance. (Fig. 284.) The chief deposits are in the cells

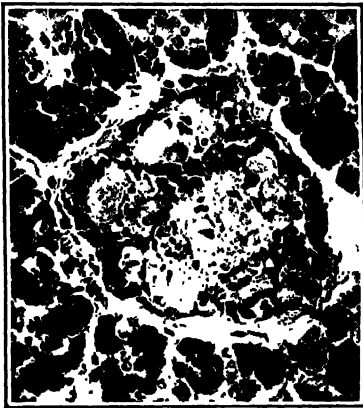


FIG. 283.—Pancreas in diabetes. The islet of Langerhans shows an extreme degree of hyaline degeneration.  $\times 325$ .



FIG. 284.—The kidney in diabetes. The clear cells of the loop of Henle are filled with glycogen.  $\times 200$ .

of the loop of Henle. (Plate XV.) The change has become much less marked since the introduction of insulin, and in many cases no glycogen can be found. The other renal change is *intercapillary glomerulosclerosis*, which is the most reliable criterion for the postmortem diagnosis of diabetes and is described on page 630.

*Lipemia* may be marked. When the blood fat is high the plasma may be milky. In exceptional cases there is a remarkable *lipoid storage* in the cells of the reticulo-endothelial system. The cells become swollen with lipoid which may take the form of globules. These large "foam cells" are seen in the spleen and liver (Kupffer cells). The lipoid is usually cholesterol ester. There may be yellow patches in the aorta and yellow nodules in the skin (xanthoma diabeticum), which are deposits of the same material. The yellow color of the skin (xanthosis) sometimes seen in diabetics is not due to lipemia but to carotin, a

pigment contained in carrots and other vegetables. There is a carotinemia, and the serum is bright yellow. The coloration of the skin is best seen in the nasolabial folds and on the palms of the hands and soles of the feet.

*Arteriosclerosis* is common in elderly diabetics. Great narrowing of the pancreatic artery may aggravate the disease by cutting down the supply of blood to the islets. The vessels of the limbs are narrowed and calcified, so that *dry gangrene* is common in the legs of elderly patients. The large amount of sugar in the tissues probably lowers their resistance and favors bacterial infection. Narrowing of the coronary arteries often leads to severe myocardial degeneration. The renal arteries and kidneys may be affected. Old diabetics more often die nowadays from the results of the arteriosclerosis than from the diabetes.

**Cystic Fibrosis.**—The condition originally known as cystic fibrosis of the pancreas (Anderson) is now recognized to be a systemic disease of childhood with a variety of clinical appearances, the occurrence of which depends on the time at which the lesions occur and on which organs are affected (Farber). The most striking lesions occur in the pancreas. Usually that organ is firmer and thinner than normal, but it may show no gross change or may be nodular. The acinar tissue is atrophied and replaced by fibrous tissue. The small and large ducts are dilated and filled with homogeneous eosinophilic material like inspissated secretion, and the acini may contain similar material. The mucous glands of the trachea and bronchi are also filled with inspissated material, and a similar condition prevails in the salivary glands, duodenum, jejunum, and gall-bladder. The dilatation of the pancreatic ducts may lead to cyst formation. The obstructive lesions of the pancreas may result in two quite dissimilar pictures in infancy and childhood, depending on the time of onset of the lesions. If pancreatic achylia occurs during the latter part of intra-uterine life the result is an inspissated meconium which may cause intestinal obstruction shortly after birth (meconium ileus). If the achylia does not develop for a few weeks after birth the clinical picture is one of severe nutritional deficiency closely resembling celiac disease. Respiratory symptoms may dominate the picture; these are due to obstruction of the bronchi and bronchioles by thick tenacious mucus, which eventually leads to bronchiectasis. A marked degree of squamous metaplasia may be associated with the bronchiectasis, but the relationship of one to the other is obscure.

In one of my cases, a boy seventeen years of age in whom this metaplasia reached an extreme degree, there was marked coarsely nodular cirrhosis of the liver. In this case the acinar tissue of the pancreas was entirely replaced not by fibrous tissue but by fat. Some of the symptoms seem to be due to defective absorption of vitamin A, but it is a mistake to attribute the fundamental lesions to a congenital deficiency of this vitamin. Farber points out that the widespread involvement of mucus-secreting structures suggests a possible deficiency of the mucinase required for the maintenance of mucus in a normal physical state, a deficiency which may be due to autonomic imbalance in the nervous control of secretion in the pancreas and in mucous glands.

**Other Pancreatic Cysts.**—These may be congenital cysts, cystadenomas, or pseudocysts. *Congenital cysts* are rare, and are part of congenital cystic disease involving the kidneys and sometimes the liver. *Cystadenomas* are rare tumors which may be benign or malignant. *Pseudocysts* are the common variety, but they are not true cysts of the pancreas and have no epithelial lining. They are usually situated in front of the pancreas in the lesser sac of peritoneum. They may attain a large size. The cyst is preceded by some injury to the pancreas, either trauma or acute hemorrhagic pancreatitis, as a



result of which the pancreatic secretion escapes into the lesser sac, and as the foramen of Winslow becomes sealed a cyst develops. The fluid may be clear and serous, or yellow or brown from hemorrhage. The fluid may contain pancreatic ferments, but their absence does not mean that the cyst is not of this nature, for they often disappear.

### CALCULI OF THE PANCREAS

These small stones in the pancreatic duct are rare. They consist of calcium and phosphate. They may cause obstruction or bacterial infection.

### TUMORS OF THE PANCREAS

**Carcinoma.**—This is the only common tumor of the pancreas. Like other cancers of the digestive tract, it is much commoner in men than in women. At least 70 per cent of the cases occur in the head of the pancreas. (Fig. 285.) This part of the gland is enlarged and



FIG. 285.—Carcinoma of the head of the pancreas causing marked displacement of the second part of the duodenum.

remarkably hard. The hardness may simulate chronic pancreatitis, and the surgeon may find it difficult or even impossible to distinguish between the two conditions at an exploratory laparotomy. *Microscopically* the tumor may arise from the ducts or the acini. The duct tumor, which is far the commoner, is an adenocarcinoma; the columnar cells have clearly defined margins, a vesicular nucleus and a distinct nucleolus. In the acinar cell type there are lobular masses of polyhedral or rounded cells, with poorly defined cell margins, large hyperchromatic nuclei, and no visible nucleoli. Secondary growths occur in the regional lymph nodes and liver. The symptoms depend on the location of the tumor. In cancer of the head of the pancreas the chief symptom is persistent and increasing jaundice, due to pressure on the opening of the common bile duct. The bladder is dilated and thin-

walled in accordance with Courvoisier's law. In cancer of the body and tail spread is a more striking feature, and this influences the symptoms (Duff). Deep-seated gnawing pain is due to spread along the perineural lymphatics, ascites is caused by implantation growths on the peritoneum or involvement of the portal vein, and distant metastases are more common than in cancer of the head.

*Secondary carcinoma* is not common in the pancreas. There may be invasion from the stomach, gall-bladder or bile duct. In rare cases there may be metastases from hypernephroma and other tumors.

*Adenoma*.—These tumors are rarely seen, but Warren suggests that this is because they are so small that they are overlooked at autopsy. They are composed of acinar tissue and are definitely encapsulated.

**Tumors of the Islets of Langerhans.**—This is an uncommon but very interesting group. The tumor is usually innocent (adenoma), but cases of carcinoma have been reported. In several cases the adenoma has been successfully removed at operation, and its nature has been proved by the demonstration of the specific granules of islet tissue and by the recovery of insulin from the tumor mass. A simple way to distinguish between tumor cells and acinar cells is to stain the zymogen granules of the latter; this is much easier than to stain the specific granules of the islet cells. It has been suggested that these lesions are in the nature of heterotopia rather than adenoma; this would serve to explain the occasional presence of duct-like structures, absence of encapsulation and apparently invasive growth (Holmes *et al.*). Sometimes there is a diffuse hypertrophy of the islet tissue throughout the pancreas rather than a localized adenoma. These cases naturally do not lend themselves to operation. The *symptoms* are those of hyperinsulinism or insulin shock with marked hypoglycemia due to overactivity of the islet tissue and overproduction of insulin. There may be attacks of faintness and unconsciousness when the interval after a meal is too long, and these can be averted by taking sugar. The condition is therefore the reverse of diabetes.

### OBSTRUCTION OF THE PANCREATIC DUCT

Obstruction may be caused by cancer of the head of the pancreas, a gall stone impacted at the ampulla of Vater, a pancreatic calculus, or cicatricial contraction. The ducts become irregularly dilated, the acini atrophy and disappear and are replaced by fibrous tissue. The islets of Langerhans are unaffected, and as the pancreas shrinks in bulk, these structures appear to be more numerous and stand out with great distinctness. It was by producing experimental obstruction of the pancreatic duct by means of ligature that Banting and Best first succeeded in freeing the islet tissue from the trypsinogen-producing acini and were thus enabled to extract insulin. Carcinoma of the head of the pancreas may occasionally produce exactly the same effect. (Fig. 286.)

### HEMOCHROMATOSIS (BRONZED DIABETES)

This rare condition has already been considered in Chapter II. It is a disorder of iron metabolism characterized by the most extreme hemosiderosis. The pancreas is of a rich brown color. Both the acinar tissue and the islets are loaded with granules of hemosiderin, so that they give an intense Prussian blue reaction. A slow process of necrosis occurs in the damaged cells, and gradually they atrophy, disappear, and are replaced by fibrous tissue. As the islets are destroyed as well as the acinar tissue, diabetes develops.

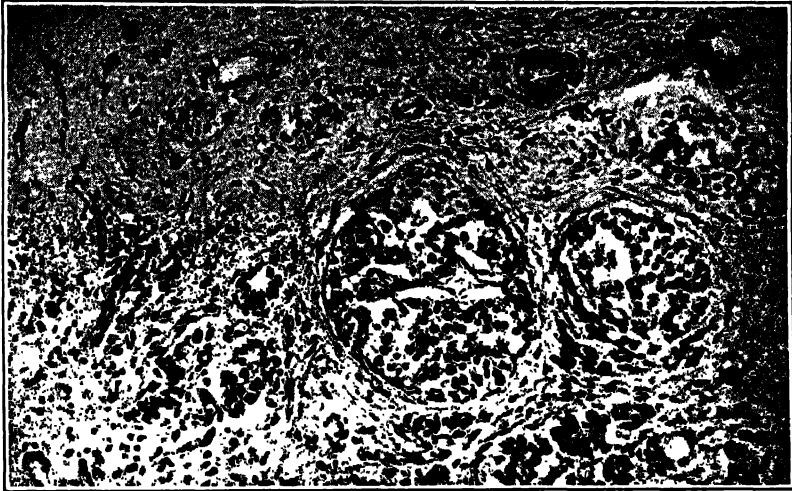


FIG. 286.—Almost complete disappearance of acini due to obstruction of the pancreatic duct. The islets remain intact.  $\times 150$ .

### OTHER LESIONS OF THE PANCREAS

**Tuberculosis.**—This is a rare condition. Even in general miliary tuberculosis the pancreas seldom shows tubercles. A primary lesion is almost unknown, and spread from a neighboring focus (lymph node, etc.) is almost equally rare.

**Syphilis.**—In *congenital* syphilis the pancreas often contains large numbers of spirochetes. The acini are poorly developed, their place being taken by cellular connective tissue. *Acquired* syphilis is uncommon and usually takes the form of a diffuse fibrosis. A gumma of the pancreas is extremely rare.

**Lipomatosis.**—This is merely a local manifestation of obesity. Large fat cells occupy the interstitial tissue, and if the lipomatosis is extreme it may cause some atrophy of the acinar tissue.

**Congenital Anomalies.**—Malformations of various kinds may occur. The best defined of these is the condition known as *annular* or *ring pancreas*, in which the head of the pancreas surrounds the second part of the duodenum and may cause some constriction. Of more importance is *heterotopia of the pancreas*, a condition in which accessory pancreatic tissue is found in the pyloric end of the stomach, the duodenum, and more rarely in the ileum and even the mesentery.

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## CHAPTER XXIII

### THE PERITONEUM AND ABDOMINAL WALL

#### THE PERITONEUM

##### ACUTE PERITONITIS

**Etiology.**—Acute inflammation of the peritoneum is the result of bacterial infection, although a local reaction may be caused by such aseptic irritants as a strip of gauze or a drainage tube, and a more general reaction by hemorrhage or the escape of fluid from a cyst. The common bacteria found are *Bacillus coli* and streptococci; less frequent are staphylococcus, pneumococcus, gonococcus, *Bacillus pyocyaneus*, *Bacillus typhosus*, and certain anaerobic bacilli. The most acute and diffuse cases are those due to streptococci.

The infection may reach the peritoneum in three ways. (1) *From an abdominal organ.* This is much the commonest way, and the usual source is the gastro-intestinal canal. Appendicitis easily heads the list, followed by gastric, typhoid, and dysentery ulcers, ulcerating carcinoma, etc. When the bowel becomes strangulated (hernia, etc.) or when it is gangrenous from infarction, peritonitis quickly develops. When the infection comes from the hollow viscera there may either be perforation with an outpouring of intestinal contents (ruptured appendix, perforated gastric ulcer), or the bacteria may pass through the intact but inflamed wall of the bowel. It is evident that in the former case the resulting peritonitis is more likely to be widespread and overwhelming. The female pelvic organs form a second important group, of which the principal members are puerperal sepsis, which is nearly always streptococcal, and gonococcal infection of the Fallopian tubes, which usually causes a local inflammation limited by adhesions. Other occasional sources of infection are acute cholecystitis, hemorrhagic pancreatitis, abscess of the liver, etc. (2) *From the exterior.* This may be due to an accident, or may occur in the course of a surgical operation. (3) *Hematogenous* infection is very rare; it is seen in the secondary form of pneumococcal peritonitis.

**Morbid Anatomy.**—Peritonitis is at first a local condition. It may remain local or may become diffuse. At first the membrane merely appears pink and injected. Then the normal sheen is lost and replaced by a frosted appearance, due to the formation of a layer of fibrin on the surface. Finally the coils of bowel are glued together by a sticky exudate. Meanwhile a fluid exudate is being formed, and collects especially between the adherent coils of bowel. At first it is serous, but soon it becomes purulent. A thick creamy exudate is a better sign than a thin seropurulent one, which always suggests severe

streptococcal infection with low resistance and a bad prognosis. Hemorrhagic fluid is seen in infarction of the bowel, strangulations, etc. The *microscopic appearance* is that of an inflamed serous membrane. The chief element of the exudate in the early stages is fibrin, but if the condition becomes purulent there may be a thick layer of polymorphonuclear leucocytes together with a variable number of red blood cells. The surface endothelium may be desquamated, but even in severe cases it sometimes remains intact under the exudate.

**Spread.**—Spread may occur over the surface or *via* the lymphatics. *Surface spread* tends to be limited by protective adhesions, and by the action of the great omentum, which plays the part of the abdominal policeman, spreading itself over the inflamed area, sealing up a threatened perforation, and generally acting the part of guardian to the hollow viscera. It effectively prevents many a case of local peritonitis from becoming general. When the omentum is found in an abnormal position and adhering to a viscus, it is safe to assume that trouble is brewing. *Lymph spread* takes place with great rapidity in the subserous lymphatics in streptococcal infections, much as the infection spreads in cryptipelas.

The great *danger* of general peritonitis is *paralytic ileus* rather than septicemia, for inflammation tends to seal the channels of absorption. If a coil of ileum hangs down so as to dip into a pool of pus in the pelvis it will become paralyzed and be as completely obstructed as if a ligature had been tied around it. The proximal part of the small bowel becomes acutely dilated and its lumen is soon filled with highly toxic material. Symptoms of acute intestinal obstruction with toxic absorption are now added to the picture, but are apt to be obscured and overlooked with fatal consequences. The surgeon cannot attack and drain a generally infected peritoneal cavity, but he can relieve the distended small bowel by inserting a tube. It has been well said that "if the bowels can be made to act, the patient recovers; if they fail to act, he dies."

The *end-results* are complete recovery, the formation of fibrous adhesions, or death. The question of adhesions is considered later. They are not always permanent and may sometimes disappear.

**Varieties of Peritonitis.**—The pyogenic microorganisms responsible for acute peritonitis give rise to lesions which have many features in common, but some of the main types may be considered separately.

**Bacillus Coli Peritonitis.**—*Bacillus coli* peritonitis is the commonest variety, but it is complicated by streptococcal infection more often than is suspected, for when cultures are made from the exudate the streptococci are completely overgrown by these coliform organisms. Much more accurate information is afforded by smears of the exudate than by culture. The exudate in pure *Bacillus coli* infections is usually thick and purulent, and has a characteristic fecal odor. This form of peritonitis is less fatal and fulminating than several of the others.

**Streptococcal Peritonitis.**—Streptococcal peritonitis is very virulent. Spread takes place in the subperitoneal lymphatics, and in this way

infection sweeps from one end of the abdomen to the other. The exudate is thin and serous or slightly purulent, odorless, and contains little fibrin, so that the coils of bowel are not gummed together. Smears of the fluid show chains of streptococci which are not contained within the cells of the exudate. In *Bacillus coli* peritonitis, on the other hand, smears usually show many bacilli lying within the phagocytes.

**Pneumococcal Peritonitis.**—This variety is in a class by itself and should be separated in the mind from the other forms of acute peritonitis. It may be *secondary* to a primary focus elsewhere, usually in the lung or middle ear. The mode of infection is either by the blood stream or through the diaphragm.

The *primary form* occurs principally in childhood, but I have seen a case in a woman aged sixty-two years. McCartney and Fraser, in a study of 56 cases, did not find a single example in a boy. It is a disease of the poorer classes, and is probably due to lack of cleanliness. McCartney and Fraser have shown that infection may occur by way of the female genital tract, thus explaining the peculiar sex incidence. The statistics of the Hospital for Sick Children, Toronto, provide an interesting contrast to those which have just been quoted. Of 39 cases of proved primary pneumococcal peritonitis, 30 were females and 9 were males. The mortality in the females was 53 per cent and in the males 77 per cent. These figures will be greatly lowered by the introduction of the sulphonamide drugs. The usual age incidence is between the third and seventh years.

The disease begins as a pelvic peritonitis but the infection rapidly spreads. The fimbriae of the tubes are congested and pus containing pneumococci can be expressed. The exudate is at first watery, containing flakes of fibrin. It is only later that it becomes purulent.

**Gonococcal Peritonitis.**—Gonococcal peritonitis is a disease of the female, the infection passing along the Fallopian tube. In rare cases it may follow infection of the seminal vesicles in the male. The peritonitis usually remains confined to the pelvis, and after a short acute phase soon becomes chronic, but occasionally the inflammation may be general. Its chief characteristic is the formation of very dense fibrous adhesions in the pelvis.

**Localized Peritonitis.**—It is not usual for inflammation of the peritoneum to become generalized. Unless the infection is overwhelming, as in perforation of a hollow viscus or gangrene of the bowel which allows ready passage of enormous numbers of bacteria, there is a tendency for the process to be localized. Two things may happen. (1) The inflammation may pass off and the membrane return to a normal state, or there may be thickening and adhesions. (2) Pus may be formed, which is limited by adhesions to form an abscess such as the periappendicular abscess which follows acute appendicitis. It is unusual for such an abscess to open into the peritoneal cavity; it is more likely to discharge onto the skin surface or into a hollow viscus. These localized peritoneal abscesses are often seen in the female pelvis. A special form is the subdiaphragmatic or subphrenic abscess.

A *subphrenic abscess* is a collection of pus between the diaphragm above and the liver, stomach, or spleen below. In most of the cases the original inflammatory focus is in the upper part of the abdomen, especially gastric and duodenal ulcer and abscess of the liver, but the pus may trek up from below, *e. g.*, appendicular abscess, pelvic abscess. The site of the initial focus of infection determines whether the abscess be under the right dome of the diaphragm or the left. The abscess is shut off from the general abdominal cavity by adhesions. Usually the pus is intraperitoneal, but when the primary lesion is in the appendix, liver, or kidney the pus is retroperitoneal. The diaphragm is pushed up on the affected side as shown by the roentgen-rays and the liver is pushed down. The condition is progressive, and the abscess may burst into the peritoneal, pleural, or pericardial cavities.



FIG. 287.—*Lycopodium granuloma* showing spores, giant cells and fibrosis.  $\times 75$ .

***Lycopodium Peritonitis.***—*Lycopodium* spores in the dusting powder of surgical gloves may cause a localized peritonitis with the formation of adhesions or large numbers of small surface nodules which may be mistaken for tubercles or carcinomatosis. The surface of the spore (the edge as seen in a section) is furnished with firm spicules which cause it to adhere to any surface with which it comes in contact, and to be forced beneath that surface by any manipulation. The lesions consist of lymphocytes, plasma cells

and foreign body giant cells which may contain the acid-fast spores. The whole forms a *lycopodium granuloma*. (Fig. 287.) Similar lesions are produced by talc powder, which consists of crystals of magnesium silicate, and appear as refractile bodies in the lesion.

***Tuberculous Peritonitis.***—The peritoneum is infected with tuberculosis either from an abdominal organ or from outside the abdomen. There are three chief intra-abdominal sources: (1) tuberculosis of the bowel, (2) tuberculous mesenteric glands, and (3) tuberculosis of the Fallopian tube. In the first and third of these the infection may be limited to a few tubercles on the outside of the intestinal ulcer or the infected tube. We are concerned here with general infection of the membrane. Repeated infection may occur through the ostium of the tube, so that no treatment is of avail until the tube is removed, but usually the ostium is sealed up by adhesion of the fimbriæ. The extra-abdominal sources are the lungs and pleura (probably lymph spread through the diaphragm), and a distant focus in bones, joints, or bronchial lymph nodes (blood spread). The disease is commoner in children and young adults, and occurs in two main forms, the moist and the dry.

In the *moist form* the chief feature is the great distention of the



abdomen, with its tight shiny dome overtopping the wasted body of the patient. The distention is caused by a great accumulation of thin, watery, pale yellow fluid which shows the characteristics of an exudate, *i. e.*, a specific gravity above 1018 and an albumin content about 4 per cent. It contains many lymphocytes and may be blood-stained. Blood in the abdominal fluid suggests tuberculosis or malignancy of the peritoneum. When the fluid is removed the surface of the peritoneum is seen to be studded with miliary tubercles. Sometimes the tubercles excite the formation of a plastic exudate which covers up and hides the tubercles. There may be larger caseous masses and the mesenteric lymph nodes are usually large and caseous. The omentum may be thick and contracted, but this is more characteristic of the dry form. Occasionally the fluid may be encysted by adhesions, so as to simulate an abdominal cyst. Opening of the abdomen and drainage of the fluid is often followed by remarkable improvement which it is difficult to explain, but unless the primary focus (Fallopian tube, etc.) is removed a permanent cure cannot be expected. The injection of oxygen into the peritoneal cavity also gives good results.

In the *dry form* there is little or no fluid, but a dense plastic exudate is produced which glues the intestines together and is followed by the formation of very firm adhesions. When the abdomen is opened the coils of intestine are matted together and cannot be separated, so that a detailed examination of the bowel for tuberculous ulcers may be a matter of great difficulty. The surface may be studded with tubercles, but often these are completely covered by the inflammatory exudate. The omentum is thickened and contracted so that it forms a flat mass like a pancake or a rounded one like a sausage which can be felt through the abdominal wall. When the coils of bowel are partially separated collections of fluid may be found between them. A fecal fistula may be formed owing to a loop of diseased bowel becoming adherent to the abdominal wall, followed by caseation of the wall and ulceration of the skin surface. The fistula may open at the umbilicus.

### TUMORS OF THE PERITONEUM

**Secondary Carcinoma.**—The peritoneum may be infected from carcinoma of any intra-abdominal organ. There may be one or two masses in the mesentery and omentum, or a condition of diffuse carcinomatosis. The primary tumor is usually in the stomach, large bowel, or ovary (malignant papillary cystadenoma). The infection is caused by the tumor perforating the serous coat and scattering cells over the serous surface. The connection between the tumor on the inside and the tumor on the outside may be very evident to the naked eye, or the process of serous invasion may be only seen with the microscope. Tumor cells from a cancer of the stomach may drop down through the peritoneal cavity, forming little implantations on the serous surface to mark their track, and becoming seeded on the pelvic organs where they may form large secondary growths. The ovaries

form particularly favorable soil, and may present large tumors before a cancer of the stomach is suspected. Lymphatic spread may result in widespread dissemination. In such cases the wall of the bowel may be covered with a fine network of white lines representing lymph vessels distended by tumor cells. The irritation of the peritoneum causes ascites to develop, and carcinoma cells may be found in the fluid. Unless the cells are in clumps it is very unsafe to diagnose them as indicating malignancy. The fluid is often hemorrhagic.

If the primary tumor is a colloid type of carcinoma, the secondary growths form large soft jelly-like masses. The curious condition of *pseudomyxoma peritonei* may be caused by rupture of a pseudomucinous cyst of the ovary and more rarely of a mucocele of the appendix. This condition, which is not really malignant, is considered in connection with ovarian cysts.

*Primary tumors* are so extremely rare that they need only be mentioned. It is said that a primary endothelioma of the peritoneum may occur in the form of a diffusely infiltrating tumor.

**Retroperitoneal Tumors.**—These are rare tumors growing from the retroperitoneal connective tissue of the posterior abdominal wall. The chief of them is the lipoma and sarcoma.

*Retroperitoneal lipoma* is really a mixed tumor, although consisting largely of fat. Some parts are myxomatous and some sarcomatous. It commences at one side of the vertebral column, usually at the level of the kidney, grows very slowly, and may reach an enormous size, filling the greater part of the abdominal cavity. It may creep through the intervertebral foramina and compress the cord. The tumor is more nearly related to the teratomata than to an innocent lipoma, and may occur in early childhood, although usually in middle age.

*Retroperitoneal sarcoma* is a fibrosarcoma which grows from the fascia of the posterior abdominal wall. It shows the usual gross and microscopic characters of a fibrosarcoma.

### MESENTERIC CYSTS

Cysts of the mesentery and omentum are rare. *Lymphatic cysts* of the mesentery are probably lymphangiomata of congenital origin. They occur in childhood and early adult life. They are usually single and about the size of a hen's egg, but may attain a great size. The lining is a flat endothelium, and the contents are watery or milky. *Gas cysts* of the mesentery are very rare, though common in the pig. They are quite small and are usually grouped in one segment of the bowel. Their nature is uncertain; the gas may be formed by bacteria, or may be produced by cells. *Hydatid cysts* are fairly common in the mesentery, where they form multiple masses which may reach a large size.

### ASCITES

Ascites is an accumulation of serous fluid in the peritoneal cavity, so that the abdomen becomes converted into a bag of fluid (*askos*, a bag). The fluid may be dropsical in origin, *i. e.*, a transudate, or inflammatory, *i. e.*, an exudate. *Dropsical ascites* may be part of a general dropsy due to cardiac or renal disease, or it may be due to obstruction of the portal vein. Portal obstruction is usually caused by portal cirrhosis of the liver, but may be due to pressure on the vein

by a tumor, enlarged glands, etc. The *exudative form* of ascites is caused by irritation of the peritoneum by tuberculosis or carcinoma-tosis, and the fluid may contain blood. Ascites in a woman with normal heart and kidneys should suggest carcinoma of the ovaries. The inflammatory fluid has a higher specific gravity (above 1018) and protein content (above 3 per cent) than the dropsical fluid.

**Pick's Disease.**—This condition has already been discussed under the heading of chronic constrictive pericarditis, but it is mentioned here because the most striking features may be great thickening of the peritoneum and recurring ascites. In one case which I examined when the abdomen was opened it looked as if the viscera had been removed, so marked were the pressure effects of the ascites and so great was the peritoneal thickening. There is often a polyserositis, affecting peritoneum, pericardium, and pleura.

## THE ABDOMINAL WALL

The abdominal wall suffers from the same pathological conditions as the rest of the surface of the body, but a few lesions deserve separate mention.

**Tumors.**—A *lipoma* of the subcutaneous tissue is not uncommon. It must be differentiated from small extrusions of extraperitoneal fat in the middle line of the epigastric region.

The *fibroma* or *desmoid tumor* grows from the sheath of the rectus and tends to infiltrate the muscle. It is densely hard, and interlacing bands of fibrous tissue are seen on the cut surface (*desmos*, a band). About 80 per cent of the cases occur in women who have borne children. In the remaining cases there is usually a history of injury to the abdominal wall. The enclosed muscle fibers may become converted into multinucleated plasmodial masses like giant cells. Some of these tumors show a tendency toward malignancy, recurring repeatedly after removal.

**Actinomycosis.** When the cecum or appendix is the seat of actinomycosis, the infection may spread to the overlying abdominal wall, appearing as a hard swelling in the right groin. This softens and discharges pus containing the characteristic sulphur granules.

**Ossification of Abdominal Wall.**—In rare cases bone may be formed in the scar of a laparotomy wound. This usually occurs above the umbilicus, and appears to be an example of metaplasia of one form of connective tissue into another form. It has also occurred in the hypogastrium following operations on the bladder (prostatectomy, etc.). This is more readily understood, for Huggins has shown that bladder mucosa transplanted into the abdominal wall gives rise to bone formation, although with no other mucous membrane was a similar result obtained.

**Lesions of Umbilicus.**—The umbilicus, though a small structure, suffers from many diseases, as may be seen in Cullen's monograph of 650 pages. The most important lesions are congenital anomalies, fistulæ and tumors.

**Patent Vitelline Duct.**—The vitelline or omphalo-mesenteric duct, the original communication between the intestine and the yolk sac which normally becomes closed at the end of the second month of intra-uterine life, passes from the ileum a short distance above the ileocecal valve to the umbilicus. When the intestinal end remains open it is called *Meckel's diverticulum*; this is a common condition. Rarely the entire tract remains open, so that the intestine communicates with the surface; this is known as a patent Meckel's divertic-

ulum. The distal end only may remain open while the intra-abdominal part is obliterated; the mucous membrane is prolapsed on the surface to form a raspberry-like tumor. If both ends are closed but the intervening portion remains open, a cyst is formed.

*Patent Urachus.*—The urachus is the communication between the urinary bladder and the allantois *via* the umbilicus. If it does not become obliterated, there is a fistulous opening at the umbilicus through which urine is discharged. A urachal cyst is formed if both ends of the duct are closed but the intervening part remains patent.

*Fistulæ.*—Examples of fistulæ of *congenital* origin have already been described. An abdominal *abscess* may point and rupture at the umbilicus. A *fecal fistula* is most often due to tuberculous peritonitis, a loop of diseased bowel becoming adherent to the umbilicus; caseation and breaking down then give rise to a fistula between the bowel and the skin.

*Tumors.*—Tumors of the umbilicus are usually *secondary carcinomas*. The primary growth is likely to be in the stomach, large bowel, gall-bladder or ovary, and is usually an adenocarcinoma. It feels like a hard button. The tumor cells may reach the umbilicus *via* the round ligament. Secondary cancer of the umbilicus is a late manifestation, and indicates that the case is inoperable.

*Primary carcinoma* is very rare, although I happen to have seen 3 cases. It is usually an epidermoid carcinoma, but may be an adenocarcinoma. It is probable that most of the latter cases reported in the literature are really secondary. *Endometrioma* is an interesting tumor, in the form of a small red nodule from which blood may be discharged at the menstrual period. It consists of endometrial tissue (see discussion on Endometriosis). It is also known as an adenomyoma, because it may contain both glandular and muscular tissue.

#### ADDITIONAL READING

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**Lycopodium Peritonitis.** ACTOPOL: Arch. Path., 1933, **16**, 326. ERB: Surg., Gynec. and Obst., 1935, **60**, 40.

**Pneumococcal Peritonitis.** MCCARTNEY AND FRASER: Brit. J. Surg., 1922, **9**, 479.

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**Talcum Granuloma.** FIENBERG: Arch. Path., 1937, **24**, 36.

## CHAPTER XXIV

### THE URINARY SYSTEM

#### THE KIDNEYS

**Descriptive Outline.** --It is of particular importance in describing so complex an organ as the kidney that a definite order should be followed, otherwise essential points may be omitted. These points are as follows: size, weight, consistence, capsule, cortex, medulla, arteries, pelvis. The *size* is fairly constant in health; if only one kidney is present it will be twice the normal size and weight. The length is about 11 cm., the breadth 6 cm., and the thickness 3 cm. The kidney substance may be divided into lobules by deep grooves, a condition known as fetal lobulation and of no pathological significance. The average *weight* is 150 grams. The *consistence* is such that when held horizontally by the middle, each end tends to dip slightly. If softer than normal, the kidney may form the arc of a circle when held by the middle. If the consistence is increased (amyloid), there is no dipping even when it is held at one end. The *capsule* is thin, translucent, and can be readily stripped off, leaving a smooth surface. If it has become adherent as the result of disease, pieces of cortex may come away when attempts are made at removal (decortication). The *cortex* between the base of the pyramid and the capsule is 5 mm. wide; the deep cortex lies between the pyramids. The color of the cortex is reddish-brown; it may be pale due to ischemia, yellow due to lipoid deposits or fatty degeneration, or dusky red due to congestion. The cortex is traversed by fine alternate red and gray lines, best seen by means of a hand lens. The red lines correspond to the interlobular vessels, the gray lines or medullary rays to the collecting tubules and parts of the loop of Henle passing down into the medulla. These cortical markings become distorted or completely lost in chronic Bright's disease. The boundary zone of the *medulla* shows a continuation of the cortical markings. The papillæ projecting into the pelvis are inspected for early lesions of tuberculosis. The condition of the *arteries*, best seen at the base of the pyramids, is noted; their walls are thickened in hypertension. The *renal pelvis*, with a capacity of 7 to 10 cc., is lined by a smooth, glistening, grayish-white mucous membrane in which no vessels should be visible.

The *microscopic description* includes glomeruli, tubules, interstitial tissue, and arteries. Each glomerulus consists of a glomerular tuft, a capsular space, and Bowman's capsule lined by flattened epithelium. The glomerular tuft is made up of capillary loops, each of which presents a basement membrane lined by endothelium and covered by epithelium, the latter being continuous with the epithelium lining Bowman's capsule and with the tubular epithelium. The juxtaglomerular apparatus is a collection of cells at the vascular pole of the glomerulus in relation to the afferent arteriole, possibly concerned with the regulation of blood flow through the glomerulus.

#### BRIGHT'S DISEASE

In 1827 Richard Bright described a series of cases in which edema was associated with the presence of albumin in the urine, and which he correctly attributed to disease of the renal parenchyma, though

guided by naked-eye examination alone. With the passage of time the conception of what was called Bright's disease became greatly widened, at least on the pathological side, so that now a number of different chronic inflammatory and degenerative conditions are included which bear a clinical resemblance to one another but which have a different pathological basis. It seems useful to retain the term Bright's disease, if only for sentimental reasons, and to include in it the three conditions known as glomerulonephritis, nephrosis, and nephrosclerosis (the arteriolosclerotic kidney); to these must now be added the contracted stage of pyelonephritis.

### GLOMERULONEPHRITIS

Diffuse glomerulonephritis is an inflammatory condition affecting the glomeruli primarily, but with secondary damage to the other parts of the nephron as well as the interstitial tissue later. It is the condition which should be understood when the word nephritis is used without qualification. The glomerulonephritis is diffuse in distinction to other less important forms of focal glomerulonephritis. The pathology and symptomatology of glomerulonephritis vary to such an extreme degree that three different forms have been described under the names acute nephritis, subacute or subchronic nephritis (formerly called chronic parenchymatous nephritis), and chronic nephritis (formerly chronic interstitial nephritis). Thanks to the work of Löhlein, Volhard and Fahr, Bell, and others, it is now possible to say that, from the pathological point of view, these are three stages of the same process. It is true that in very many cases it is difficult or impossible to detect a transition from one to the other clinically, so that the patient may show merely the third stage or the second stage, but not infrequently a patient will pass in orderly fashion through the three stages, the clinical picture thus corresponding with the pathological lesions. These stages are the acute, the intermediate and the chronic.

The *acute stage* is characterized clinically by urinary evidence of acute inflammation, signs of acute renal insufficiency, edema, and a varying degree of hypertension. In the *intermediate stage*, also called *subacute* and *subchronic*, there is edema and albuminuria. The chief features of the *chronic stage* are hypertension and renal failure. Recovery is usual after the first stage, but repeated subinfections may cause the kidney to pass through all three stages if the patient survives long enough.

**Etiology.**—*Acute diffuse glomerulonephritis* is an indication of *bacterial infection*, but this infection is extrarenal and not within the kidney. In almost every case the infection is due to *streptococci*. Different strains may act as the causal agent, *e. g.*, the hemolytic streptococci of scarlet fever, the non-hemolytic streptococci of subacute bacterial endocarditis, and streptococcal sore throat. The scarlet fever cases form a well-defined group in children. The most striking feature is the fact that it is really a postscarlatinal nephritis, for it comes on

from the second to the sixth week, when the acute infection has passed away and the temperature has returned to normal. These cases usually recover completely and seldom pass into the chronic stage. The relation of sore throat and tonsillitis to acute nephritis is well marked. Sometimes an acute attack will occur after tonsillectomy or there may be an exacerbation of preëxisting symptoms. There is no relation between the severity of the throat attack and the danger of nephritis, for nephritis may follow a very mild throat infection.

Although the disease is due to streptococci, there is no actual bacterial invasion of the kidney. No bacteria are found in the tissues, and the blood and urine are sterile. When the blood and kidney are flooded with bacteria, as in streptococcal septicemia from acute ulcerative endocarditis, the effect is not diffuse glomerulonephritis but focal pyemic abscesses. The inflammatory lesions in the glomeruli are the result of toxins, which always produce more diffuse lesions than do bacteria. In the acute first stage very few glomeruli are spared.

The latent interval observed in postscarlatinal nephritis suggests that immunological reactions of an allergic character may be concerned. The same interval is often seen between tonsillitis and an attack of acute nephritis. Duval and Hibbard found that the toxins of scarlatinal streptococci only produced nephritis in the rabbit when they were first acted on by immune serum, so that apparently some allergic change is necessary before the toxins are able to act as an irritant to the glomeruli.

Cold is undoubtedly a predisposing factor, especially a combination of cold and wet. There seems to be a close relation between the vessels of the skin on the one hand and those of the kidney and throat on the other. When the skin of an animal is chilled there is a transient albuminuria, due probably to vasoconstriction of the glomerular capillaries followed by dilatation. It is known that chilling of the body surface causes vasoconstriction and ischemia of the mucous membrane of the throat (Mudd and Grant), and these changes may lower resistance and excite infection. These facts when taken together suggest an explanation of the part which cold occasionally plays in the etiology of acute nephritis.

The *nephrotoxic serum* of Masugi produces renal lesions in animals bearing a marked resemblance to those of human glomerulonephritis. The "nephrotoxin" is not a toxin but a specific antibody which acts only on the kidney. It is prepared by immunizing animals of one species with a suspension of perfused kidney tissue obtained from a second species. This antiserum induces nephritis when injected into members of the species which supplied the kidney tissue. It is of clinical interest to note that diet had a profound effect both on the course of the nephritis and on the pathological lesions. On a low protein-high carbohydrate diet all the animals (rats) recovered, whereas on a high protein-low carbohydrate diet they all succumbed to chronic progressive nephritis. The seat of the greatest tubular damage in the high protein group was the proximal convoluted tubule.

In *chronic* glomerulonephritis it is much more difficult to determine the etiological agent. In order that the nephritis may become chronic it seems that there must be some extrarenal focus of infection from which the kidney is subjected to repeated infections or rather repeated intoxications. A history of recurrent sore throat is often obtained. In other cases no history of infection can be elicited, but here also the pathological evidence shows clearly that the lesion is an inflammatory one and must have been caused by a "cryptogenic" infection.

**Symptoms.**—The symptomatology of glomerulonephritis is so diverse that little is to be gained by giving a list of symptoms at this stage. Some of the principal ones will be discussed when the relation of symptoms to lesions is considered. It may be useful, however, to indicate some of the possible courses which the disease may follow. The clinical picture may vary to such a degree that it is difficult for the observer to convince himself that the different patients are merely suffering from variations of one central theme. The chief of these variations are as follows. (1) The patient may die of uremia early in the *acute stage*, with marked albuminuria, hematuria, edema, slight hypertension, and retention of non-protein nitrogen in the blood. A not uncommon cause of death at this stage is left ventricular failure, the explanation of which is uncertain. The majority of the *acute* cases recover completely in the course of a few months. (2) He may survive the acute phase of the attack, but the features of the first stage may continue or become more pronounced until uremia develops and the patient dies in the course of a few months. (3) The acute attack is often followed by a latent period when the patient considers himself well, but after some months he presents marked edema and albuminuria with only slight hypertension (sometimes none) and no impairment of renal function. He has passed into the *intermediate* or *subacute stage*. Such cases will often be wrongly diagnosed by the clinician as nephrosis, although it is permissible to speak of a nephrotic stage, provided the word be used in a clinical and not in a pathological sense. Sooner or later hypertension and impairment of renal function make their appearance, often with a coincident disappearance of the edema. The duration of the intermediate stage is variable. Usually within a period of two years the patient either dies of an intercurrent infection, to which he is very susceptible, or passes into the third stage. In some cases, however, the stage of edema lasts for many years. (4) The majority of patients in the *chronic stage* present no history of an acute attack. The blood-pressure rises gradually as renal insufficiency increases; this is in striking contrast to essential hypertension in which high levels are attained early in the disease. A history of cerebral hemorrhage or coronary heart disease is rare, again in marked contrast to essential hypertension. The blood non-protein nitrogen shows a slow progressive rise until the terminal stage, when the rise becomes sudden. The average time between the acute attack and death in the chronic stage is about ten years, but it may be much shorter or considerably longer. The different type and stages are so interwoven that it is dangerous to attach simple labels to them, but in a general clinical way it may be said that the *first stage* is the stage of *acute urinary disturbance*, the *intermediate* is the stage of *edema*, and the third is the stage of *hypertension* and *chronic renal insufficiency*.

**Lesions.**—*Acute Glomerulonephritis.*—Both kidneys are always involved in diffuse glomerulonephritis. The gross appearance is not specially characteristic. The kidneys are usually swollen, and the capsule is tense. The pale cut surface suggests cloudy swelling.

*Microscopically* the essential lesions are in the glomeruli. Practically all the glomeruli are involved, so that it is a true diffuse nephritis; such a picture could only be produced by the action of a diffusible



toxin. The glomeruli are swollen so as completely to fill the capsular space. They are much more cellular than normal, for reasons which will soon become apparent.

The best idea of the process is to be obtained by a consideration of one of the capillary loops of which the glomerular tuft is composed. (Fig. 288.) The whole of the pathology of glomerulonephritis can be studied in a single loop, and all the other changes of the first, second, and third stages follow as a natural consequence. Each loop is covered



FIG. 288.—Glomerulus, showing individual units, the capillary loops of which the tuft is composed, widely separated.  $\times 400$ .

externally by a layer of epithelium and lined internally by endothelium. In ordinary preparations it is not easy to distinguish between these two types of cell, but the distinction becomes much easier when the fine basement membrane of the loop which separates the two sets of cells is stained with Mallory's aniline blue. The epithelial cells lie outside the membrane, while the much less numerous endothelial cells lie inside the membrane. (Plate XVI, A.) The epithelial cells show the first change. They become swollen and multiply so as to fill in the spaces between the loops. Later they undergo degeneration and are

cast off into the capsular space. The changes in the endothelium are of much greater importance. They become much swollen, multiply greatly, and tend to block the lumen of the loop. (Plate XVI, *B*.) The capillary obstruction is still further increased by the formation of fine intercapillary fibers which are apparently derived from the basement membrane of the capillary loops. In the chronic stage these fibers fuse together and convert this part of the tuft into a dense hyaline mass. In addition to these proliferative changes, polymorpho-



FIG. 289.—Glomerulonephritis, showing endothelial proliferation and avascularity of the tuft. The case is in the intermediate stage; epithelial crescent above.  $\times 450$ .

nuclears collect in the glomerular capillaries, and there is a varying amount of exudate (serum, fibrin, leucocytes and red blood cells) in the capsular space. Shaw Dunn believes that the earliest change is a uniform dilatation of the glomerular capillaries, which is responsible for the escape of albumin and red cells into the urine.

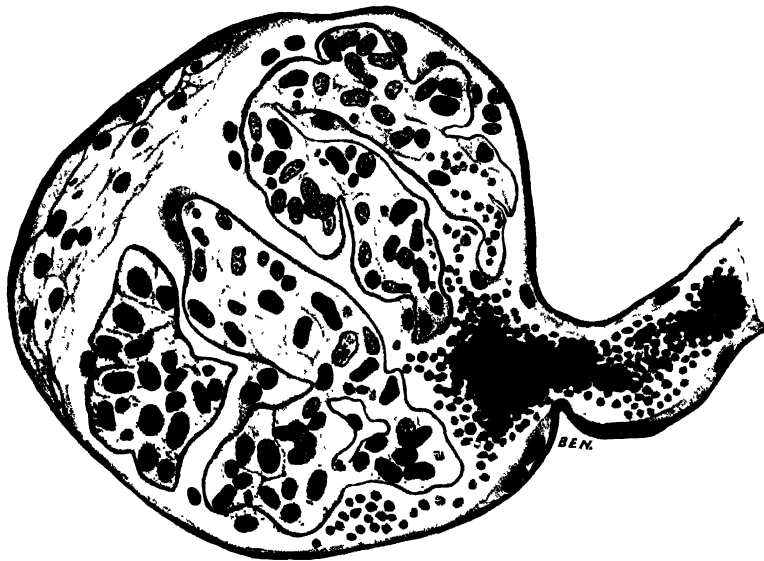
As a result of the proliferative changes the loop becomes occluded and bloodless. (Fig. 289.) The other loops of the tuft share in the change, with the result that little or no blood flows through the glomerulus. This glomerular ischemia accounts for the hypertension

## PLATE XVI



### Normal Glomerulus.

The capillary loops show numerous epithelial cells, a few endothelial cells, and the basement membrane. (Azocarmine.)



B

### Glomerulonephritis.

The lumen of the capillaries is almost entirely filled with proliferated endothelial cells. There is an epithelial crescent at one side. The capsular space and the tubule contain red blood cells. (Azocarmine.)



which accompanies the acute stage of nephritis. The blood supply to the tubules passes through the glomeruli, so that the ischemia will lead to secondary tubular degeneration and in turn to increase of the interstitial fibrous tissue. These changes, however, are not seen in the first stage of nephritis. The tubules, apart from some cloudy swelling, the interstitial tissue, and the arteries are for practical purposes normal.

The *further course* may be toward *healing* or *chronicity*. In the scarlatinal cases there is usually complete recovery, and if the patient dies some years later the glomeruli may show no trace of former lesions; in other cases a greater or less number of glomeruli are found to be obliterated. In the few cases in which chance or accident has given the pathologist an opportunity to study the process of healing, removal of the exudate blocking the capillaries seems to take place in the same way as resolution of a lobar pneumonia. The exudate is gradually absorbed and the ischemic glomeruli become filled once more with blood. In other cases, especially those due to streptococcal infections of the throat, the kidney is exposed to repeated reinfection, so that the process advances to the second and finally the third stage of nephritis. As regards the microscopic changes the *first stage* is the stage of *proliferation*, the *second* is the stage of *degeneration*, and the *third* is the stage of *atrophy* and *scarring*.

*Subacute Glomerulonephritis*  
(*Chronic Parenchymatous Nephritis*).

—The gross appearance is well described by the old term “large white kidney.” (Fig. 290.)

The kidney is slightly or considerably enlarged, the capsule strips easily, and the exposed surface is smooth and pale. The cut surface shows marked swelling and pallor of the cortex, in comparison with which the pyramids appear unnaturally dark. The pallor is due chiefly to a great accumulation of lipoid in the cells of the convoluted tubules, but in part to emptying of the capillaries from swelling of the parenchyma. There may be bright yellow streaks and patches in the cortex due to large deposits of lipoid. The consistence is soft.

*Microscopic examination* shows a picture of degeneration combined with a varying degree of the proliferation of the first stage and the atrophy and scarring of the third stage. It is naturally impossible



FIG. 290.—Kidney in the intermediate stage of glomerulonephritis; the large white kidney.

to draw too hard and fast a line between the different stages, and one part may show more proliferative lesions, while another part shows atrophy. The intermediate stage differs from the acute in the important respect that all three of the main constituents of the kidney are involved—glomeruli, tubules, and arteries—as well as the interstitial tissue.

The *glomeruli* show an advancement of the changes of the first stage. The degree of vascular occlusion probably determines the clinical course. The more severe and widespread the occlusion, the more quickly will the kidney pass into the atrophic stage. Some of the glomeruli are converted into structureless hyaline masses through which no blood can pass and which can secrete no urine into the tubules. The hyalinization is due to a gradual increase of the hyaline fibers which begin to be formed in the acute stage.

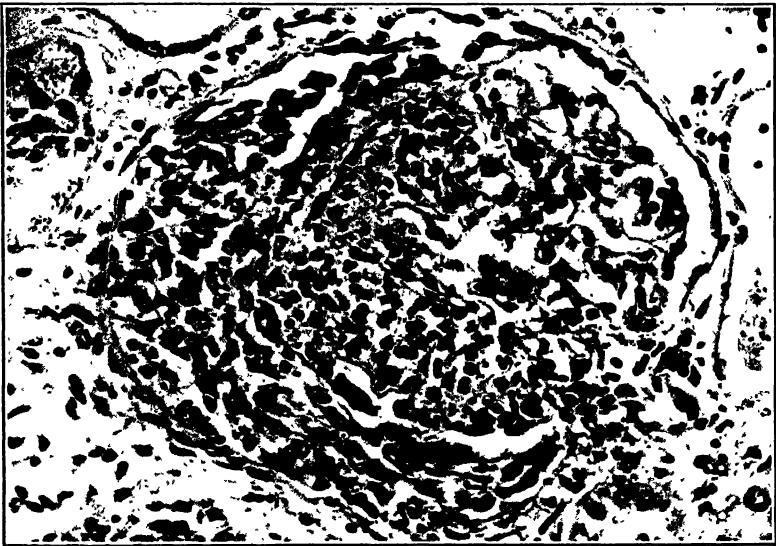


FIG. 291—The epithelial crescent of glomerulonephritis. The space between the tuft and Bowman's capsule is occupied by proliferated epithelial cells.

*Capsular changes* are also present. Red blood cells, desquamated epithelium, albumin, and fibrin are present in the capsular space in varying amount. The chief change is a proliferation of the capsular epithelium. Large masses of cells are formed which occupy the capsular space. The whole circumference of the glomerulus is seldom involved, so that the cells form a semilunar mass in the capsular space which is known as the *epithelial crescent*, and provides the most easily recognized evidence of glomerulonephritis. (Fig. 291.) In course of time the crescents become fibrosed and fuse with the hyaline tuft.

The *tubules* show marked degenerative changes, which are most pronounced in the convoluted tubules. The epithelium of the con-

voluted tubules shows cloudy swelling, fatty degeneration or necrosis. The fat content may be very high. In addition to neutral fat the cells may contain large amounts of lipid material, chiefly cholesterol ester, which can be seen as bright anisotropic globules in frozen sections under crossed Nicol's prisms. As the tubular degeneration progresses, many of the epithelial cells are cast off and the tubules become atrophic.

*Chronic Glomerulonephritis (Chronic Interstitial Nephritis).* This is the *stage of scarring*. In the literature it is described as the small white kidney, granular contracted kidney, secondary contracted kidney, and chronic interstitial nephritis. In an advanced case the kidney is small and shrivelled, its surface is covered with fine granules, and the capsule is so adherent that, when it is stripped off, portions of the cortex come away with it (decortication). (Fig. 292.) The meaning of the granularity is shown by the microscopic examination. Sometimes the surface may be smooth even though the microscopic changes are marked.

The cut surface shows extreme irregularity and atrophy of the cortex, which in places may be only 1 or 2 mm. in width. The irregularity corresponds with the granularity of the surface. The normal vertical markings of the cortex produced by the vasa recta are lost. The pyramids are normal. The pelvis may be dilated owing to the general atrophy, and there is an increase of the pelvic fat outside the epithelial lining.

*Microscopic examination* shows almost complete loss of the renal architecture. The parenchyma, which normally consists practically entirely of tubules with a few scattered glomeruli, has been replaced by the cheap substitute of fibrous tissue. It is this disappearance of tubules which strikes the observer most on first examining the section.

The *glomeruli* shows hyalinization in its most extreme form. Owing to the disappearance of the tubules and the shrinkage of the cortex there may be large numbers of hyaline glomeruli in a low-power field. (Fig. 293.) Other glomeruli are atrophic and shrunken, but their capillaries still allow the passage of some blood. Were it not so, the



FIG. 292. — Chronic glomerulonephritis (granular contracted kidney).

patient could not have survived. An occasional epithelial crescent may remain in the unhyalinized glomeruli to indicate a still active inflammatory process, but in the cases of long standing they have usually all disappeared or become fibrosed and fused with the tuft. The hyaline glomeruli fade away and blend with the surrounding tissue until they can no longer be distinguished. The arteries, which may also become greatly fibrosed and thickened (see below), do not disappear in this way.

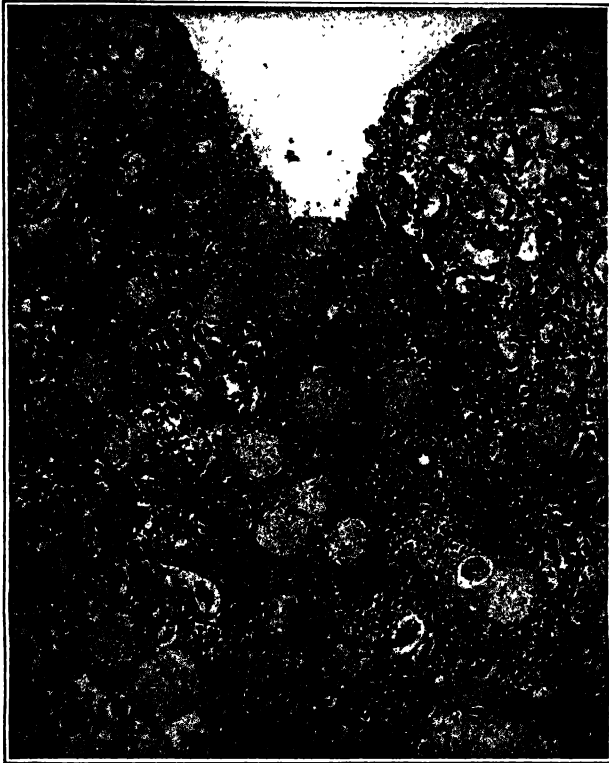


FIG. 293.—Complete hyalinization of glomeruli with disappearance of tubules in center of field and round-cell infiltration.  $\times 60$ .

The *convoluted tubules* show an extreme degree of atrophy, and only their outline may be detected under the high power. Some of the tubules appear normal or more often are dilated and lined by a high epithelium with papillary buds projecting into the lumen, although when the dilatation is marked the cells become low or even flattened. These tubules, which are connected with more or less normal glomeruli, may be regarded as showing evidence of compensatory or work hypertrophy. They are collected in little groups which stand out in striking contrast to the rest of the shrunken parenchyma, and it is these islands



of tubules which, projecting above the surrounding surface, give rise to some of the granularity. The collecting tubules are atrophied, but to a much lesser degree.

The *interstitial tissue* shows a very great increase, which is mostly apparent due to the concentration of tissue, but to some extent is real. This is the feature indicated by the unsatisfactory term chronic interstitial nephritis. Groups of small round cells may form a striking picture in the fibrosed cortex especially in the neighborhood of the hyalinized glomeruli.

The *arteries* supplying the fibrosed atrophic areas show the changes of disuse atrophy, the chief feature of which is marked fibrous thickening of the intima causing narrowing of the lumen. This is a form of endarteritis obliterans similar to the change which occurs when a vessel is ligated. If hypertension becomes marked, hypertensive vascular lesions may develop (see page 408), some of which unfortunately may resemble those of disuse atrophy. The chief of these hypertensive vascular lesions is arteriosclerosis with marked narrowing of the lumen. This may have two effects: (1) by causing renal ischemia it may accentuate the hypertension, which in turn leads to further arteriosclerotic ischemia, so that a vicious circle is set up; (2) by depriving the remaining nephrons of their blood supply it may add the *coupe de grâce* to the already faltering kidney and bring about its final downfall.

Oliver, and before him Jores and Oertel, have pointed out that in the terminal stage of Bright's disease there is a profound qualitative as well as quantitative change in the kidney. Not only are large numbers of nephrons atrophied; many of the remaining ones become hypertrophied. By using the old methods of wax reconstruction and microdissection of macerated specimens Oliver has been able to show that a hypertrophied unit may replace in physical size 15 destroyed units, and it is by means of these hypertrophied units that the patient continues to live. The remaining glomeruli become much enlarged, but by far the greatest hypertrophy occurs in the proximal convoluted tubule, which is increased in length as well as in diameter. Moreover, by means of microdissection it is found that the integrity of the tubule is not necessarily dependent on the integrity of the glomerulus, as is commonly supposed. A hypertrophied tubule may be attached to a completely atrophied and fibrosed glomerulus, and some of the tubules have been cut off from their glomeruli by scar tissue, a condition analogous to the aglomerular kidney of certain fishes.

**The Relation of Symptoms to Lesions.**—It is convenient to consider the case of a patient who passes through all three stages of glomerulonephritis. A bare outline of the varied symptomatology will first be given, and a few of the more prominent symptoms will then be picked out for discussion.

The *acute stage* is characterized by pain in the back, fever, edema, a slight rise in the blood-pressure, urinary changes such as oliguria, high specific gravity, the presence of albumin, blood and casts, and a low urea content, with a corresponding rise in the non-protein nitrogen of the blood. The *intermediate stage* is the stage of edema; it is *wet nephritis*. The chief symptom

is edema which may be extreme, and the chief urinary change is marked albuminuria with casts. The renal function shows little sign of impairment in spite of the extensive damage to the kidney, a condition of compensated renal hypofunction (Fishberg). Secondary anemia is common. The blood chemistry changes are commonly those associated with nephrosis, *i. e.*, high blood cholesterol, lowered serum albumin, and a reversal of the ordinary albumin-globulin ratio. The non-protein nitrogen of the blood is normal. The basal metabolic rate is low. This stage may be called the nephrotic stage, for the symptoms and blood and urinary findings are identical with those of nephrosis. The patient will not die of uremia, owing to compensation of the renal hypofunction, but he is likely to die of ascites, or of some intercurrent infection, especially pneumococcal peritonitis. In the *chronic stage*, that of *dry nephritis*, the edema disappears, and hypertension and nitrogen retention occupy its place. It is the stage of renal insufficiency or decompensated renal hypofunction, and the line which separates it from the second stage is a functional rather than an anatomical one. Albumin and casts may be present in the urine in small amount, but the characteristic feature is the low fixed specific gravity. Death is due to uremia, or to myocardial failure or cerebral hemorrhage from the hypertension.

Only a few of the symptoms of glomerulonephritis will be considered. Some can be explained, at least partially, by the lesions; others cannot. The latter should prove more stimulating for future enquiry than the former. The urinary changes are those which first attract the eye, but some of the most important symptoms are extrarenal. As an old writer remarks: "the good physician trusteth not the single witness of the water if better testimony be had. For reasons drawn from the urine alone are as brittle as the urinal."

*Albuminuria* is of glomerular origin, although it is most marked in the second stage which is characterized by tubular degeneration. The tubules may also add albumin to the urine as it passes through them. It seems probable that the essential cause of the albuminuria is interference with the renal filter in the glomerulus. The epithelial investment of the capillary loops may be the chief constituent of this filter, which normally prevents the proteins of the blood from entering the urine. The permeability of the renal filter is a very delicate affair which may be interfered with by processes which leave no anatomical trace. Mere clamping of the renal artery for thirty seconds will cause albuminuria due to the permeability being altered by the temporary asphyxia. The proteins of the blood plasma consist of albumin and globulin, but only the albumin escapes into the urine. As a result of this, continued and massive albuminuria will not only greatly lower the total quantity of the plasma protein; it will also bring about a reversal of the normal albumin-globulin ratio of 3 to 1. This is well seen in chronic nephrosis and in the nephrotic or second stage of glomerulonephritis. As Dunn has shown, there is another factor to be considered. In the nephrotic kidney there is a fixed patency of the glomerular capillaries, as a result of which there is a loss of their normal rhythmical contractility, so that many more glomeruli are in operation at the same time. As the same amount of blood still goes to the kidney each tuft is perfused at a much less rate than in the case of an active tuft. The result is a permanent stage of stasis with slight capillary dilatation, a condition which in other parts of the body allows an increased escape of plasma protein. The supposed degenerative changes in the tubules may be due to increased absorption of protein and lipoids, which are deposited in the walls of the tubules.

*Casts* are formed of albumin from the glomerulus, and contributions of epithelium and granular and fatty detritus from the tubules. If there is much inflammatory exudate or hemorrhage in the capsular space the casts will be coated with leucocytes or red blood cells. It is in the tubules that the casts are molded into shape.

*Edema* is probably an extrarenal phenomenon, and its explanation is not to be found in the kidney. The idea is gaining vogue that acute glomerulonephritis is a generalized capillary disease and not merely confined to the

capillaries of the renal glomeruli. Edema may set in very early, sometimes synchronously with the albuminuria, so that it seems we must look outside the kidney for its explanation. Impaired renal function of itself does not cause edema. When both kidneys are removed so that no urine can be secreted, the animal does not develop edema, but removes the water by extrarenal means. Even in health 40 per cent of the water excretion is done without the assistance of the kidney. A patient with complete mechanical obstruction of both ureters does not become dropsical. It is true that oliguria (diminished output of urine) is associated with renal edema, but it is a result of the edema and not a cause.

Renal edema may be divided into nephritic edema and nephrotic edema. *Nephritic edema* occurs in acute glomerulonephritis. It is evidently due to an increased permeability of the capillaries, because the fluid in the tissues contains over 1 per cent of protein, a condition which Eppinger has called "albu-

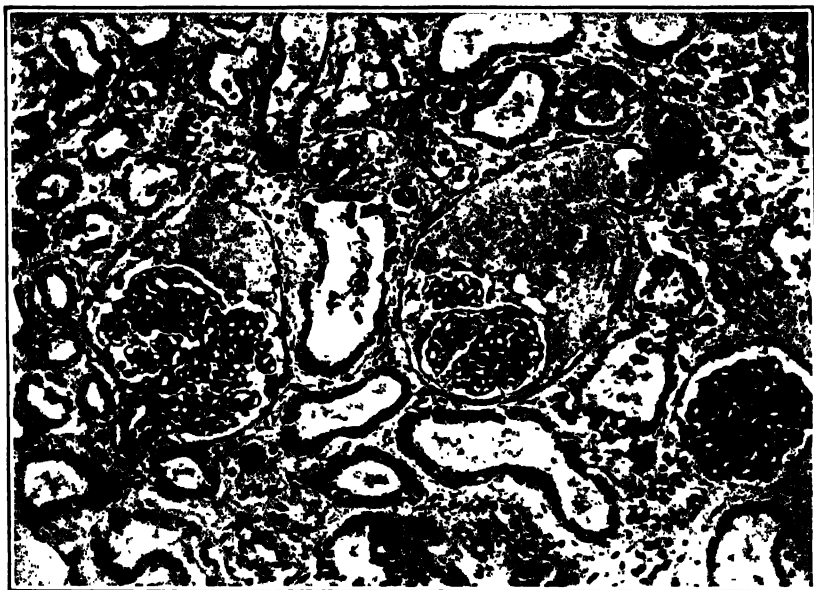


Fig. 294.—Albuminous fluid in the glomerular space in a case of nephrotic edema.  
× 150.

minuria into the tissues." The capillaries of the subcutaneous tissue are probably injured by the same toxins which act on the capillaries of the glomeruli. It is therefore an inflammatory form of edema. *Nephrotic edema* occurs in so-called chronic nephrosis, in the nephrotic or second stage of glomerulonephritis (wet nephritis), and in the amyloid kidney. The protein content of the dropsical fluid here is less than 0.1 per cent, *i. e.*, one-tenth that of nephritic edema. It is evident that the mechanism of production of the edema must be quite different. Here there is great loss of plasma protein through the heavy albuminuria (Fig. 294) with particular loss of the albumin as shown by the reversed albumin-globulin ratio. The colloid osmotic pressure of the plasma is therefore diminished, and fluid is free to escape into the tissues.

A common accompaniment of renal edema is *retention of chlorides*, but it is not a primary cause of edema. There is great salt retention in anuria due to obstruction, when the kidneys have been removed experimentally, and in the third stage of glomerulonephritis, but edema does not develop, for the

chloride accumulates in the blood, not in the tissues. The old idea of a salt-retaining kidney as the cause of chronic renal edema is a myth. Although chloride retention is not a primary cause of edema it does act as a secondary one. Once edema is established the chlorides pass out into the tissues with the water. There is what Fishberg calls a pre-renal deviation both of water and salts into the tissues. Here the salt increases the osmotic pressure and helps to keep the water bound in the tissue spaces. This explains the very beneficial effect of restricting the salt in the diet. Although we have spoken of chloride retention it appears that salt edema is due to the sodium ion, not the chloride ion as is commonly supposed. It is the sodium which moves with the water.

It is a curious but easily explained fact that chronic renal edema varies inversely with the degree of impairment of renal function. As long as a patient in the second stage of glomerulonephritis shows little or no sign of renal insufficiency, the edema is marked. When renal insufficiency develops, the edema disappears. The reason is that when renal failure sets in, the albuminuria diminishes, the blood proteins rise with an accompanying increase of the colloid osmotic pressure, and the fluid is drawn from the tissues back into the blood.

No reference has been made to the cardiac edema which may develop in consequence of the increasing hypertension and cardiac failure. It is evident that this may materially complicate the picture which has been drawn above.

*Hypertension*, moderate in degree, occurs in about one-third of the acute cases. It becomes much less and sometimes disappears entirely in the second stage. In the third stage it forms one of the dominating features, but seldom attains the extreme degree seen in essential hypertension, and usually remains under 200 mm. The hypertension is evidently of renal origin, and it is to be presumed on the basis of Goldblatt's now classical work that it is due to renal ischemia. It is possible that the *juxtaglomerular apparatus* may have some influence on the blood-pressure. This structure, as its name indicates, is situated at the vascular pole of the glomerulus in relation to the afferent arteriole. Although readily recognized in any ordinary section of the kidney, it has escaped notice in the past. The cells contain granules, which, however, are only evident in perfectly fresh and perfectly fixed material. They are much more abundant in the animal than the human kidney. Goormaghtigh claims that in experimental hypertension in the dog produced by renal ischemia the apparatus quickly undergoes hypertrophy and shows an increase in the granules. It may be that this structure, which closely resembles the cutaneous myo-arterial glomus, regulates the blood flow through the glomerulus and is related to hypertension. Observations on human kidneys have so far been disappointing, and in my own material by far the largest juxtaglomerular apparatus occurred in a young man with normal blood-pressure.

*High blood urea*, which may be taken to indicate a retention of non-protein nitrogen in general, is due to insufficiency on the part of the renal glomeruli. It is moderate in the first stage, disappears in the second stage, and may become extreme in the third stage. Its presence does not necessarily indicate the presence of nephritis, for it may be due to extrarenal causes such as the production of more urea than can be excreted (leukemia, etc.). Even when renal in origin there may be no nephritis, for in the stasis or cardiac kidney associated with a failing circulation the blood urea nitrogen may go to 40 or higher. If the congestion can be relieved, the urea drops, owing to reestablishment of the glomerular circulation.

*Blood cholesterol* is increased in nephritis with edema. It may be very high in the second stage of glomerulonephritis and in nephrosis. In acute nephritis the increase is moderate, while in the third stage it is normal or below normal. The meaning of the increase is not known. It is possibly due to some extrarenal disturbance of lipid metabolism. Although associated with edema it does not appear to be related to it. The distinction between nephritic and cardiac edema is sometimes quite difficult. Here the blood cholesterol is of

great value, for while high in nephritic edema it is normal in the edema of heart failure.

*Uremia* is a symptom-complex too varied in its manifestations to be considered here in detail. (1) The symptoms may be *cerebral*, with excitement, apathy, muscular twitchings, convulsions, and coma; (2) they may be *gastro-intestinal*, with vomiting and diarrhea; or (3) they may be *pulmonary*, with the dyspnea of acidosis. The condition is evidently a toxemia, but the nature of the toxin is unknown. Although always associated with the retention of urea in the blood, it is not caused by the urea. It is probable that different toxic products of metabolism may be at work in different cases. Uremia is the final manifestation of renal failure. Occasionally it is a cause of-death in acute nephritis. It constitutes the usual termination of the chronic stage. Tiredness, both physical and mental, is a characteristic feature of chronic uremia. When tissues from a case of uremia are fixed in a solution of xanthydrol in glacial acetic acid, masses of crystals of xanthydrol urea are found in the cerebral cortex and other organs (xanthydrol reaction). (Fig. 295.) The brain in uremia usually shows marked edema (wet brain). Uremic enteritis and pericarditis may be found at autopsy. The entire alimentary canal may be affected (dry and glazed tongue, foul mouth, uremic breath, stomatitis, enteritis). Necrotizing and ulcerative lesions are commonest in the lower part of the small intestine and the colon. Some workers believe that the lesions are due to urea retention; others say that they are unrelated to urea retention and caused by infection of mucosal hemorrhages (Jaffé and Laing).

*Anemia* is very constant, particularly in the second stage. Its cause is unknown. Probably the formation of red cells or of hemoglobin is interfered with. The chief fall is in hemoglobin, and the prognosis can be guided by watching the progress of that fall.

The *urinary changes* have already been indicated. They depend entirely on the stage. In the first stage the albumin, cellular casts, and blood indicate the acuteness of the inflammation. A few red cells may occasionally be found in the second and third stages, and may be taken to indicate a continuation or recurrence of the inflammation. The albuminuria of the second stage has already been discussed. Anisotropic, *i. e.*, doubly-refractive bodies, may be found in the urine in the second stage by means of Nicol's prisms. They consist of cholesterol ester, and are related to the deposits of cholesterol in the renal tubules. The polyuria is merely a compensatory mechanism whereby the failing kidney tries to excrete waste products. It has lost its concentrating power, and in order that the necessary amount of solids may be eliminated, a greatly increased quantity of fluid must be poured out. The loss of concentrating power is indicated by the low and fixed specific gravity, and is largely due to atrophy of the convoluted tubules whose essential function is absorption. This atrophy in turn is caused mainly by the loss of blood supply to the tubules.

Perhaps the best tests for renal function are as follows: for glomerular function, the urea clearance test (volume of blood cleared of urea in one minute's excretion of urine); for tubular function the diodrast clearance test for tubular excretion and the urine concentration test for tubular absorption.



FIG. 295. — Xanthydrol urea crystals (dark field).  
× 300.

## NEPHROSIS

The term nephrosis is used in two different senses. To the clinician it signifies a condition characterized by marked edema, massive albuminuria, low plasma protein and very high cholesterol, lack of signs of renal failure, and normal blood-pressure. This constitutes the nephrotic syndrome rather than a disease entity, for the pathological basis may vary. To the pathologist nephrosis signifies a purely tubular or mainly tubular degenerative lesion. Two main forms can be distinguished, which may be called toxic nephrosis and lipid nephrosis.

**Toxic Nephrosis.**—This is also known as tubular nephritis, for it is the response of the tubular epithelium to toxic irritants. The toxins may be exogenous or endogenous. One of the best examples of an *exogenous* poison is mercuric chloride. The renal lesions caused by mercuric chloride poisoning are described on page 633. Other heavy metals produce similar changes. *Endogenous* poisoning is seen in obstructive jaundice and in the toxemias of pregnancy, *i. e.*, pernicious vomiting and eclampsia. Similar lesions may be seen in the infective fevers, especially those in which toxemia is marked, *e. g.*, diphtheria.

The attack falls on the specialized epithelial cells of the convoluted tubules. These are greatly swollen, sometimes to such a degree that the lumen is obstructed, the cytoplasm is highly granular, chromatolysis of the nucleus occurs, and in severe cases the entire cell may disintegrate. Hyaline droplets, so-called albuminous degeneration, may be a striking feature in some of the tubules.

**Lipoid Nephrosis.**—The majority of the patients in whom this diagnosis is made are really suffering from subacute glomerulonephritis, who happen to present a nephrotic rather than a nephritic picture. In course of time, it may be several years, this is replaced by a picture of nephritis; the edema disappears, the blood-pressure rises, and renal failure develops. In classical glomerulonephritis the glomerular capillaries are obstructed; in the nephrotic phase they are hyperpermeable to protein, obstruction developing later. The albuminuria is due to increased capillary permeability, which explains the low plasma protein, which in turn explains the massive edema and ascites that is the patient's chief complaint.

In a few cases, mostly children, there is a picture of pure lipid nephrosis, what the Germans call "genuine" nephrosis. There is no history suggesting an acute attack of glomerulonephritis, nor does the patient reach a stage of renal insufficiency. The course is marked by recurring exacerbations and remissions, or the patient may eventually recover completely. Death from pneumococcal or streptococcal peritonitis is a frequent finish. These rare cases are often regarded as being due to a primary disturbance of lipid (cholesterol) metabolism, but it seems more reasonable to look to a defect (hyperpermeability to plasma proteins) in the renal filter. When the plasma protein of dogs

is kept low by continued removal (the erythrocytes being reinjected), a typical picture of lipid nephrosis develops.

The kidneys are similar in gross appearance to those of the "large white kidney" of early subacute glomerulonephritis. They may show numerous yellow streaks and patches of lipid. *Microscopically* the striking change is the degenerative lesions of the convoluted tubules, the cells of which contain both neutral fat and cholesterol ester, the latter appearing as bright, doubly-refractive bodies when a frozen section is examined under Nicol's prisms. Hyaline droplets in the cytoplasm may be even more striking than in toxic nephrosis. There may be a generalized dilatation of the tubules, with atrophy of the epithelium.

With ordinary stains the glomeruli may appear normal, but Bell has shown that when a connective-tissue stain (aniline blue) is used, marked thickening of the basement membrane of the capillary loops can often be demonstrated. The capillaries themselves are dilated. In young children the majority of the glomeruli may be normal, only a few showing the characteristic lesion. The longer the disease lasts the more widespread and pronounced are the lesions. As the condition progresses the capillaries may be found to be very thick-walled and narrowed, so that renal insufficiency and hypertension may begin to develop.

The essential lesion in nephrosis is therefore glomerular, a dilated state of the glomerular capillaries and a hyaline change in their walls. This allows escape of protein, which is concentrated during the passage of the filtrate along the tubules. The oliguria has been explained by Shaw Dunn on a basis of the intermittent character of the glomerular action. In nephrotic conditions all the glomeruli are in continuous action and their capillaries are dilated, so that a diminished filtrate is supplied to each tubule. The filtrate is supplied to all the tubules at once instead of to a few at a time, so that the total volume of urine is diminished. This appears to be the best explanation of the oliguria at the present time.

*Renal Lesions in Toxemias of Pregnancy.*—Generalized edema of varying degree is found in over 60 per cent of normal pregnant women. This is not due to any of the usual causes of edema, and a hormonal etiology is suspected. A nephrotic syndrome (generalized edema and massive albuminuria) combined with arterial hypertension may develop in the second half of pregnancy, a condition known as *pre-eclampsia*. When convulsions are added the condition becomes *eclampsia*. The hypertension may subside permanently when pregnancy is terminated. On the other hand even mild toxemia may be followed by permanent hypertension, so that the toxemia of pregnancy is one of the causes of permanent hypertension in the female.

Renal lesions are present in every case. The kidneys are enlarged, and the cortex is swollen, cloudy, and opaque. The essential lesion is in the glomeruli, and may be called *glomerulonephrosis*, for it is degenerative rather than inflammatory in type. The glomeruli are slightly enlarged, solid, and present a solid appearance. With the

aniline blue connective tissue stain there is seen to be great thickening of the capillary basement membrane causing extreme narrowing of the lumen of the capillaries. In addition there is swelling of the epithelial cells which surround the capillaries and frequently a slight increase in the number of endothelial nuclei. The combined glomerular lesions, excellent illustrations of which will be found in Bell's monograph on renal diseases, are so characteristic that from them a correct diagnosis of eclampsia can be made even in the absence of the hemorrhagic lesions of the liver on which so much stress used to be laid, and which are by no means constant. The tubules may contain precipitated protein, but degenerative changes of their epithelium are not conspicuous. In very rare cases there is the condition known as bilateral necrosis of the renal cortex (see page 649), in which complete cortical necrosis of both kidneys is associated with thrombosis of the small arteries and arterioles with resulting uremia. The other significant lesions of eclampsia are in the liver and placenta. The liver changes are described on page 526. The characteristic change is a premature ageing, as evidenced by syncytial degeneration, together with more numerous infarcts than are found in normal pregnancy. The convulsions appear to be due to cerebral edema.

Eclampsia has been called "the disease of theories." At the present time it is believed but by no means proved that the placenta is responsible for initiating the train of pathological changes. The symptoms, including hypertension, usually disappear after delivery. The placenta may produce a pressor substance which acts directly on the arterioles, or a toxic substance acting on the glomeruli, thus causing renal hypertension. One thing is certain, and that is that vasoconstriction does occur, for it can be observed in the retinal vessels. The segment of any vessel distal to an area in spasm is known to dilate and become more permeable. Through the walls of such a segment diapedesis of red cells will occur and plasma will pour out. This is the probable basis of many of both the lesions and symptoms. If the vasoconstriction and hypertension persist for more than a few weeks, permanent vascular changes may develop and the hypertension becomes irreversible. A full discussion of the problem will be found in the monograph by Dexter and Weiss.

### ARTERIOLAR NEPHROSCLEROSIS

The condition of essential hypertension may be accompanied by degenerative and fibrotic changes in the kidneys. These changes were originally included under the heading chronic interstitial nephritis, but when they came to be differentiated from chronic glomerulonephritis, they were given such names as the hypertensive kidney, the arteriosclerotic kidney and arteriolar nephrosclerosis. The latter term describes a process, just as do glomerulonephritis and nephrosis, and therefore seems preferable. The condition has long been known as the primary contracted kidney, in contrast to the secondary contracted



kidney of glomerulonephritis. Both were originally included under the term granular contracted kidney.

Essential hypertension may continue for twenty or thirty years without any evidence of renal involvement, the patient usually dying of one of three causes dependent on the prolonged hypertension: (1) congestive heart failure, (2) coronary sclerosis, (3) cerebral hemorrhage. If he survives these accidents he may gradually develop symptoms of renal insufficiency and finally die of chronic uremia. Such cases are known as benign hypertension and the renal lesions are those of benign nephrosclerosis. In a younger group of patients the hypertension may develop rapidly and pursue an acute and fatal course reckoned in months rather than years. This is the group of malignant hypertension, constituting about 10 per cent of the whole, and the renal lesions are those of malignant nephrosclerosis. The patient may or may not die of acute uremia. From a careful study of the kidney the pathologist should be able to form some opinion as to whether the patient did or did not suffer from essential hypertension, whether the hypertension was of the chronic or the acute type, and if the latter whether or not death was due to acute renal failure.

The primary renal lesion, which we believe to be the result of the high blood-pressure, is arteriolosclerosis (arteriolar sclerosis), causing ischemic atrophy of the glomeruli and tubules resembling that seen in chronic glomerulonephritis. The word arteriole is used in different senses by different workers. It is important to realize this, because it serves to explain the differences in the statistical results of different workers, such for instance as the frequency of renal arteriolosclerosis in hypertension. Some confine it to the afferent and efferent arterioles, whilst others include the distal portions of the interlobular arteries, that is to say the vessels contained within the true cortex, as contrasted with the interlobular arteries in the medulla. Either system is justifiable, but for the discussion of arteriolosclerosis it is more convenient to use the word arteriole in the wider sense, *i. e.*, as synonymous with small arteries.

Hypertension and nephrosclerosis are not synonymous. Arteriolosclerosis of the afferent arterioles always indicates hypertension, but hypertension may be present without sclerosis of these vessels in 10 per cent of cases before renal insufficiency has developed. If the interlobular arteries and afferent arterioles are taken together, sclerosis is present in 100 per cent of hypertensives, but it is also present in many elderly persons without hypertension. In cases of hypertension with renal failure sclerosis of the afferent arterioles is always present. Benign hypertension and benign nephrosclerosis are therefore not necessarily related, but hypertension acts as an accelerating factor. On the other hand malignant hypertension and malignant nephrosclerosis show a definite correlation, so that malignant nephrosclerosis may be regarded as the renal end-stage of malignant hypertension.

**Benign Nephrosclerosis.**—The *gross appearance* of the kidney depends on the duration and intensity of the vascular lesions. The kidney may appear normal even though there are marked microscopic lesions. Bell and Clawson found smooth kidneys in 75 per cent of cases of essential hypertension, although hyaline arteriolosclerosis was present in 97 per cent. In cases of long standing the kidney may be small, hard, and granular; this is the primary contracted kidney, and it may be greatly shrunken. The surface is covered with little granules produced by an alternation of pale nodules and red depressed portions.



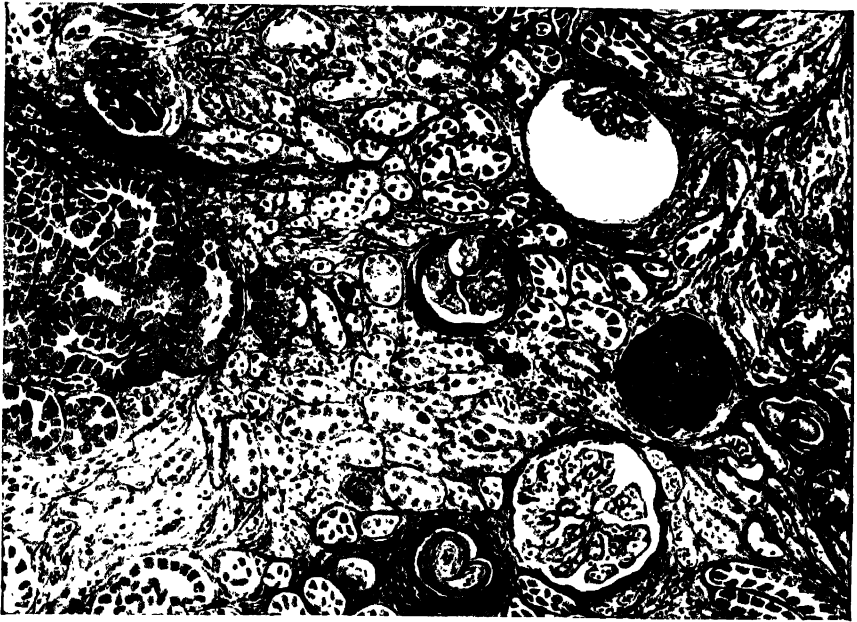
FIG. 296. —Hyaline thickening of afferent arteriole in nephrosclerosis with great narrowing of the lumen.  $\times 225$ .

The red color is due to atrophy of the cortex which allows the underlying vascular tissue to shine through. Small cysts of the surface are common. The cut surface shows irregular atrophy of the cortex and loss or distortion of the cortical vascular markings. The small arteries, especially those at the base of the pyramids, are thick-walled and gaps. The gross appearance may closely resemble that of the granular contracted kidney of chronic glomerulonephritis, but in the latter condition the granules on the surface tend to be finer owing to the diffuseness of the lesions, and the arterial lesions are not so evident. Greater shrinkage is possible than in glomerulonephritis, because the remaining glomeruli, being normal, are able to carry on renal function and maintain life. Often the distinction is impossible.

The basic *microscopic lesion* is arterial and arteriolar sclerosis.

The vascular changes of hypertension have already been described in detail on page 408. When the hypertension is of gradual development and long continued, the so-called benign form, two characteristic lesions develop in the renal vessels. These are hyaline degeneration and elastic hyperplasia. Similar changes are found in the arteries of other organs, but not to the same degree nor with the same frequency as in the kidney. *Hyaline degeneration* is best seen in the smallest vessels, such as the afferent and efferent arterioles. It is at first a smooth acidophilic thickening of the subintimal tissue, but in course of time it may involve the entire thickness of the arterial wall, leading

## PLATE XVII



### Arteriolar Nephrosclerosis.

Thickening and narrowing of the arterioles, atrophy and fibrosis of the glomeruli, degeneration of some tubules, and gradual disappearance of the remainder. One glomerulus is normal, one is shrunken, one is completely fibrosed, and one shows thickening of Bowman's capsule. (Azocarmine.)



to extreme or complete obliteration of the lumen. (Fig. 296). Fat is deposited in the degenerated tissue, so that in frozen sections stained with Scarlet Red the arterioles may appear as thick red rings. The larger arteries are often the seat of atherosclerosis. *Elastic hyperplasia* or elastosis is most marked in the larger arteries, but some degree of it may be apparent in the arterioles. When the section is stained with an elastic tissue stain it is seen that the internal elastic lamina is split into a number of layers, and the greater part of the thickened intima is composed of elastic fibers, with resulting narrowing of the lumen. (Fig. 297.)

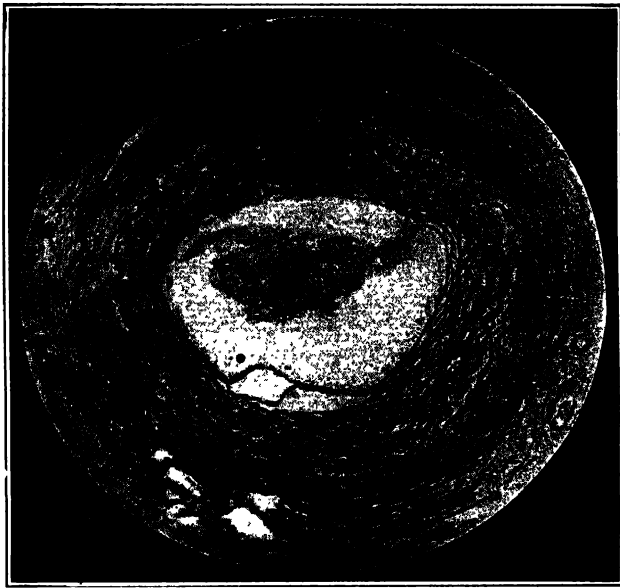


FIG. 297.—Elastic intimal thickening. Marked thickening of the inner coat with reduplication of the internal elastic lamina. (Elastic tissue stain.)  $\times 125$ .

The vascular lesions may remain the only lesions for a considerable time if the lumen of the small arteries and arterioles, the really significant vessels, is not materially narrowed. When such narrowing occurs, ischemic changes follow. Lesions of afferent arterioles affect individual glomeruli whilst lesions of larger vessels affect groups of glomeruli and tubules.

Closure of the arterioles leads to ischemic changes in the glomeruli which they supply. There is great thickening of the basement membrane (best shown by a connective tissue stain), and the entire tuft becomes converted into a hyaline mass. (Plate XVII.) At the same time the connective tissue of Bowman's capsule becomes markedly thickened, eventually fusing with the hyaline tuft and obliterating the capsular space. The corresponding tubules atrophy owing both to disuse and ischemia.

Closure of the arteries cuts off the blood supply to areas of cortex of varying size, so that wedge-shaped patches of atrophy are seen here and there. (Fig. 298.) In these areas both glomeruli and tubules have disappeared, whilst between them the tubules are normal or dilated and the epithelial lining hypertrophied. This hypertrophy and dilatation (?compensatory) is specially marked when renal insufficiency has developed, and is always suggestive of that condition. The alternation of atrophic and hypertrophic areas is responsible for the sometimes coarse granularity of the surface.

The *arterioles of other organs* may show similar changes, though not to the same degree as in the kidney. Mention may be made of the spleen, pancreas, capsule of the adrenals, liver, and brain in that order of frequency. The small vessels of the voluntary muscles are seldom affected in the ordinary benign form of hypertension.



FIG. 298.—Benign nephrosclerosis, showing a patch of atrophy with dilated tubules on either side.  $\times 60$ .

### **Malignant Nephrosclerosis: the Kidney of Malignant Hypertension.**

In over 90 per cent of cases of essential hypertension there is no serious impairment of renal function, at least for a long time. If the patient escapes death from cerebral hemorrhage or cardiac failure he may eventually die of uremia. In these cases autopsy will reveal very extensive damage to the renal parenchyma, as might be expected. But there is another group of cases in which at a younger age period (usually in the thirties and forties, sometimes in the twenties) the patient develops an acute and progressive renal insufficiency. The blood-pressure is very high, but death is likely to be due to uremia. In some cases the patient dies before the onset of uremia. Hypertensive

retinopathy, characterized by edema of the disc and retina and retinal exudates, also serves to distinguish malignant hypertension from benign hypertension with gradual renal failure. The clinical condition is one of malignant hypertension, and the corresponding renal lesions are those of malignant nephrosclerosis.

The *gross appearance* may be sufficiently characteristic to enable a diagnosis to be made with the naked eye. As a rule the kidney is of normal size and may even be enlarged whilst the surface is smooth; the *tempo* of the process has been too fast for atrophy to develop. Sometimes sufficient time has elapsed for it to become contracted and granular. Not infrequently the two kidneys differ markedly in size.

The surface may be covered with hemorrhages, usually large and blotchy (Fig. 299), sometimes small and petechial.

Microscopically the significant lesions are again in the vessels, and again they are two in number, namely, cellular hyperplasia and arteriolar necrosis. *Cellular hyperplasia*, also called productive endarteritis and hyperplastic arteriosclerosis, is the hallmark of rapidly developing hypertension. The walls of the smaller arteries are thickened by a concentric cellular proliferation, so that they may present an "onion-skin" appearance. In some cases the hyperplasia may be mainly in the intima, so as to deserve the term endarteritis, but in others it is external to the elastic lamina, and is therefore a thickening of the media. When the process is less acute the new tissue may become collagenous. Fatty degeneration may be marked in frozen sections. Elastic hyperplasia is not a special feature. *Arteriolar necrosis*, also called necrotizing arteriolitis, is best seen in the afferent arterioles. Nuclear detail is lost, the elastica disappears, the wall stains brightly with eosin, and its limits become indistinct as if red paint had been smudged across it. (Fig. 300.) Aneurysmal dilatation may occur, the necrotic wall is infiltrated with red cells, and hemorrhage is common. Arteriolonecrosis is not nearly so common as productive endarteritis, and its significance is different. It is usually an indication of renal failure, although this is not invariably the case. It appears to be a product of rapid severe hypertension coupled with the action of toxic retention products.

The various forms of arterial change may not present the clean cut picture of a text-book description; thus intimal and medial cellular proliferation may blend so that they cannot be distinguished separately. The important thing is to recognize hyperplastic small arteries and arterioles. In the chronic long-drawn-out cases the characteristic feature is hyalinization; in the more acute and rapid (malignant) forms

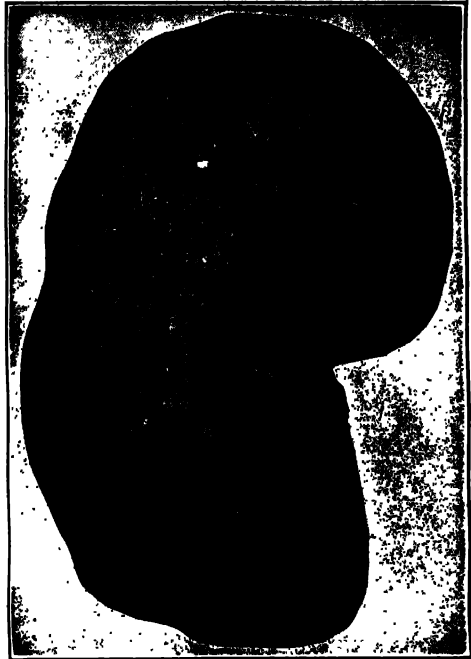


FIG. 299.—Malignant nephrosclerosis. The surface of the kidney is covered with blotchy hemorrhages.

the small arteries stand out prominently as thick-walled cellular structures with narrowed lumen.

The *renal parenchyma* does not show the advanced atrophy that is seen in the benign form owing to the quickened *tempo*. There are two features which are characteristic of renal failure and are therefore present in malignant nephrosclerosis, namely, focal degenerative glomerulitis and tubular dilatation with hyperplasia of the epithelial cells. Two features may often be observed in cases marked by rapid renal failure. These are focal glomerulitis and tubular dilatation with hyperplasia of the lining cells. *Focal glomerulitis* is characterized by fusion and necrosis of the capillary loops, swelling, degeneration (fatty, hyaline droplets, or necrosis) of the epithelium covering the tuft, and

the formation of fibrinous adhesions between the glomerular loops and the lining of Bowman's capsule. There may be patchy necrosis of the tuft with hemorrhage into the capsular space. Focal glomerulitis characterized by proliferation rather than degenerative changes (proliferation of epithelium of tuft and capsule and also of capillary endothelium) is encountered in advanced cases of benign nephrosclerosis, in chronic pyelonephritis, and even in elderly individuals in whom there is marked reduction in the renal parenchyma. It has been suggested that these

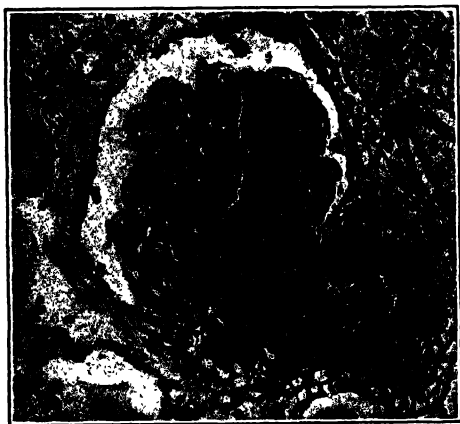


FIG. 300.—Arteriolar necrosis in malignant nephrosclerosis. The afferent arteriole and the right-hand side of the tuft show the smudgy necrotic appearance characteristic of this condition.  $\times 225$ .

glomerular changes are due to an excessive work demand on the remaining glomeruli (Gross and Morningstar). *Tubular hyperplasia*, probably compensatory in character, when present in marked degree is excellent evidence of renal failure. It is most marked in chronic glomerulonephritis, is quite pronounced in malignant hypertension, and may be present in lesser degree in benign hypertension if the stage of renal failure is reached. Fatty and hyaline droplet degeneration of the remaining tubules is common.

*Other organs* may show the characteristic hyperplastic arteriolosclerosis and arteriolonecrosis. These are most frequently seen in the fatty capsule of the adrenals or in the glands themselves, but they are also present in the pancreas, retina and brain. In the retina they may be responsible for the lesions of hypertensive retinopathy and in the brain for those of hypertensive encephalopathy.



Shapiro, as the result of injecting the kidneys in malignant nephrosclerosis with India ink, is of the opinion that the ischemia is functional, not organic, for the necrosed glomeruli were found to be filled with blood. He considers the glomerular condition to be one of hyperemia with retardation or complete stasis, similar to what happens in inflammation. The ink remains in the glomeruli, but hardly any reaches the efferent arteriole. It would appear that many apparently ischemic pictures are agonal or postmortem artefacts (Ricker).

The main features by which in characteristic cases malignant hypertension can be distinguished from the benign form are as follows. In malignant hypertension a relatively young person develops an unusually high blood-pressure (over 200 mm. Hg), papilledema is a constant feature, hematuria is common, and death is usually due to acute uremia. The kidneys are of normal size or only moderately contracted, and may show hemorrhages on the surface. The significant microscopic features are cellular hyperplasia, arteriolonecrosis, focal glomerulitis and tubular hyperplasia, the corresponding features in benign hypertension being elastic intimal hyperplasia, hyaline arteriosclerosis and hyalinization of the glomeruli.

**The Senile Arteriosclerotic Kidney.**—From the pathological point of view this condition might be called senile nephrosclerosis, but it is such miles away functionally and clinically from true nephrosclerosis (the arteriosclerotic kidney) that it would be confusing and rather misleading to give it that name. In persons over the age of fifty in whom the aorta and its larger branches show atherosclerosis, the kidneys are often contracted and grossly scarred. The condition might be called the scarred contracted kidney. The scars appear on the surface as depressions and give an impression of old infarcts. If the vascular lesions are more diffuse the kidney may be coarsely granular. The renal artery is markedly atheromatous, with narrowing of the lumen of some of its branches.

The *microscopic picture* corresponds to the gross appearance. Owing to atheromatous narrowing of the larger branches of the renal artery there are wedge-shaped areas of fibrosis where the glomeruli are completely hyalinized, and the tubules have disappeared and been replaced by fibrous tissue. The wedge-shape is caused by the fan-like distribution of the vessels. (Fig. 301.) The condition has no relation to hypertension, so that the arteriolar lesions characteristic of that state are not seen. The intervening tissue between the sclerotic areas is normal.

**The Relation of Symptoms to Lesions in Nephrosclerosis.**—In the senile arteriosclerotic kidney there is no hypertension and no renal insufficiency. The kidney is withered and scarred, but, as Clifford Allbutt puts it, it is "a starved but not a corrupt kidney, sufficient for the smaller life of an elderly man." It is not the result of essential hypertension, and as the remaining parenchyma is healthy, there is no danger of renal insufficiency.

In *benign nephrosclerosis* the patient may live for many years with no sign of renal involvement. Sooner or later there will be a lowering of the specific gravity of the urine, a loss of the concentrating power of the kidney owing to atrophy of the convoluted tubules from loss of their blood supply, and the

appearance of small quantities of albumin and occasional granular and hyaline casts. Such a kidney will show sclerosis of many glomeruli and disappearance of the corresponding tubules, but the remaining parenchyma can still be whipped up to perform the work of excretion, as is indicated by hypertrophy of the residual parts, so that there is compensated renal hypofunction but no true insufficiency. If the patient lives long enough the advancing nephrosclerosis will destroy the last remnants of parenchyma and true insufficiency will develop, but as a rule the overstrained vessels in the brain will burst, the laboring heart will suffer defeat, before symptoms of uremia have time to appear.



FIG. 301.—Wedge-shaped area of sclerosis in senile arteriosclerotic kidney.  $\times 75$ .

In *malignant nephrosclerosis* the patient may rapidly lose weight. Retinal lesions (edema, hemorrhage and patches of exudate) may be the first indication of the gravity of the condition. It is probable that arteriolar spasm, which may be observed directly in the retinal vessels, is a factor of primary importance in the production of many of the widespread lesions. As has already been pointed out in connection with eclampsia, spasm of an arterial segment is accompanied by dilatation of the segment immediately distal, and through the wall of the dilated segment diapedesis of red blood cells may occur and large quantities of plasma be poured out, giving rise to edema. This is the basis of the retinal lesions, and probably of the lesions responsible for such symptoms of hypertensive encephalopathy as transient paralysis, convulsions and finally coma. There is soon evidence of renal failure, the concentrating power of the kidney is lost, the specific gravity of the urine falls though never to the extreme

low limits of chronic glomerulonephritis, being seldom below 1.010, albuminuria may be marked and casts are constantly present, there may be red blood cells in the urine, the non-protein nitrogen is retained in the blood, and the patient dies of uremia. These lesions are due to the rapidly produced ischemic lesions of the glomeruli. The presence of the red cells in the urine is explained by the hemorrhage into the capsular spaces, which in turn is due to the necrotic lesions of the glomeruli and afferent arterioles.

**The Relation of the Kidney to Hypertension.**—Renal lesions of an ischemic nature may cause hypertension. This is seen in the secondary hypertension which develops in the course of glomerulonephritis. Goldblatt's production of persistent hypertension by means of experimental renal ischemia proves the same thing. Houssay found that transplantation of an ischemic kidney into an animal from which both kidneys had been removed was followed by persistent hypertension. Hypertension of renal origin can be produced by the method of Page, which consists of wrapping the kidney in cellophane. This soon produces a tight-fitting fibrous hull or envelope which compresses the renal parenchyma. Hypertension develops in about four weeks after application of the wrapping, even though the wrapping is unilateral. It is well known that chronic pyelonephritis may be associated with hypertension, and in rare instances only one kidney may be involved, so that nephrectomy is possible. An unusually dramatic case is that reported by MacKay and his associates at the Toronto Western Hospital. A calculus was removed from the kidney of a young man with normal blood-pressure. The wound became infected, and four weeks after operation he developed very severe cerebral symptoms and marked hypertension (200/140 mm. of mercury). A second operation showed the kidney to be surrounded and compressed by a tight-fitting hull of fibrous tissue. When this was removed the symptoms promptly disappeared, and the blood-pressure returned to normal where it has remained for a number of years.

The renal pressor substance, renin, appears to be contained in the proximal convoluted tubules, not in the distal tubules nor in the juxtaglomerular group of cells (Friedman and Kaplan). Differentiation between the two groups of tubules can be accomplished by injection of sodium tartrate, which produces necrosis of the proximal but not of the distal tubular epithelium.

The distinction between the renal hypertension of glomerulonephritis and primary hypertension may be easy for the clinician if the patient has been under observation for a considerable period. In the primary form high blood-pressure develops early, whilst renal insufficiency is a late manifestation. Papilledema (in the malignant form), cerebral hemorrhage, coronary heart disease, and congestive heart failure are common features. In glomerulonephritis hypertension develops gradually *pari passu* with renal insufficiency, and marked secondary anemia is an early feature. If the patient is seen only after uremia has developed it may be very difficult to make the distinction.

The pathological distinction may be easy or difficult. In nephrosclerosis the lesions are much more patchy than in glomerulonephritis, and the remaining glomeruli are unaffected. Epithelial crescents, which may be fibrosed, indicate glomerulonephritis. The arterial lesions of nephrosclerosis, both benign and malignant, are characteristic. A serious difficulty is presented by the fact that hypertension in the uremic stage of glomerulonephritis may cause vascular lesions identical with those of malignant nephrosclerosis. In both diseases a vicious circle may be established. Hypertension leads to arteriolosclerosis, this produces ischemic lesions, and these in turn may intensify the hypertension. This is true also of chronic pyelonephritis.

It is evident that renal lesions can produce hypertension. The mystery of essential or primary hypertension, however, still remains unsolved. Goldblatt has produced a condition apparently identical with essential hypertension in the dog by means of bilateral experimental ischemic lesions of the kidneys. The success of Wilson and Byrom with the rat is even more significant, for by means of unilateral renal ischemia they were able to produce persistent hyper-

tension together with the lesions of malignant nephrosclerosis in the other kidney, a condition which progressed even after the ischemic kidney was excised. Against this imposing mass of experimental evidence is the fact that a person may have benign hypertension without vascular renal lesions other than those incidental to any person of the same age. Even if specific vascular lesions are present there may be little or no vascular occlusion with consequent renal damage. In view of the vast bulk of normal kidney tissue remaining it does not seem likely that any minimal lesions which may be present could produce so striking a change in the blood-pressure. It is improbable that primary renal vascular disease is a common cause of hypertension in man. The kidney is the victim rather than the culprit. It appears more probable that essential hypertension is due to an unknown extra-renal factor, but that in the later stages a renal component (ischemia) plays a part as the vicious circle develops. It is possible that studies on the juxtaglomerular apparatus may throw further light on the problem.

**Interacapillary Glomerulosclerosis.**—A peculiar and distinctive degenerative glomerular lesion has been described by Kimmelstiel and Wilson occurring in long-standing cases of diabetes often associated with benign hypertension, particularly in persons over forty years of age. In the center of the tuft or



FIG. 302.—Interacapillary glomerulosclerosis.  $\times 120$ .



FIG. 303.—Kidney in multiple myeloma; cast with giant cells.  $\times 150$ .

in the center of one of the lobules there is a sharply localized hyaline mass suggestive of amyloid disease. (Fig. 302.) This is the result of a broadening of the intercapillary connective tissue. Although hypertension is usually present, it is not a necessary part of the clinical picture. The lesion is the most reliable criterion for the histological diagnosis of diabetes in persons over the age of forty. A hyaline substance, often rich in lipoid, may be deposited in the capsular space. Marked arteriosclerosis with much fatty degeneration of the arterial wall is commonly present. The clinical picture

may be nephrotic in type with massive albuminuria and marked edema, ending in uremia; in mild cases there are no renal symptoms. Although advanced lesions are found only in diabetes, they occur in less than 50 per cent of the cases, and mild lesions may be seen in old persons apart from diabetes, although these may be hard to distinguish from the more diffuse lesions of nephrosclerosis.

**Multiple Myeloma.**—In this widespread disease of bone the patient may develop anuria and die of uremia. At autopsy the renal glomeruli are normal, but the tubules are either atrophied or filled with peculiarly dense firm casts, which may excite a foreign body giant-cell reaction. (Fig. 303.) In this disease the urine may contain a peculiar form of protein known as Bence-Jones protein, and it is this which forms the casts. The tubular atrophy is caused by obstruction. Apparently the uremia has an obstructive basis.

**Transfusion With Incompatible Blood.**—When a donor of the wrong group is used for blood transfusion, the patient shows marked hemoglobinuria, and may develop anuria and die of uremia. Hematin casts are found in the renal tubules, apparently depending on acidity of the urine. The anuria has been attributed to these casts, but as they may be negligible in amount in fatal cases it seems probable that there is some other explanation. The presence of blood pigment casts in the tubules is valuable evidence that the blood used in the transfusion was incompatible.

**Crush Nephritis.**—What has been called the *crush syndrome* is a mysterious condition which has appeared as the result of air raids. The patient is buried under a mass of masonry and sustains crushing injuries to the muscles, and a few days later anuria develops, followed by death from uremia. At autopsy: no lesions have been detected in the glomeruli, but degeneration is present throughout the whole tubular system, most marked in the ascending limb of Henle and the second convoluted tubule. The epithelium shows degeneration, necrosis and regeneration. Pigment casts similar to those of incompatible blood transfusion are present in the collecting tubules. There may be an inflammatory reaction around the casts and desquamated epithelium. Similar renal lesions in patients dying of uremia have been described in war injuries. It has been suggested by Bywaters, who did the original work on crush nephritis, that the renal failure was due to blockage of the tubules by myohemoglobin casts, this pigment being derived from the injured muscle. These casts are of diagnostic value, but they are not present in sufficient number to make tubular blockage a probable explanation of the anuria. It seems more likely that renal anoxia due to hemorrhage, hypotension and other factors, damages the sensitive renal epithelium, with resulting renal failure.

**Sulphonamide Nephritis.**—The most important cause of death in patients treated with the sulphonamides is anuria and renal insufficiency. In many cases this is due to a state of natural or induced hypersensitivity to the drug (Rich). The general subject of sulphonamide allergy is discussed on page 145. The two striking renal lesions are a nephrotic degeneration of the epithelium of the convoluted tubules and a focal interstitial nephritis. (Fig. 304.) The anuria may be attributed to the tubular lesions, which are similar to those seen in incompatible blood transfusion and the crush syndrome. It is from the interstitial lesion that the pathological diagnosis can be made. There are small areas of focal necrosis, associated with which are collections of inflammatory cells, chiefly macrophages, plasma cells, and often large numbers of eosinophils, the latter always suggestive of an allergic lesion.

**Renal Anoxia.**—Renal failure, usually associated with oliguria, may develop in a bewildering variety of extrarenal conditions in which it may prove a fatal factor. Examples of such conditions are shock, burns, trauma, intestinal obstruction, incompatible blood transfusion, blackwater fever, and the crush syndrome. It may develop as the result of crush injuries to the liver and operations on the gall-bladder, in which case it is known as the *hepato-renal syndrome*. It has occurred in war injuries without crushing. The onset of oliguria is often the first symptom, and is always a sign of ill-omen. The condition has been called the *renal syndrome*, traumatic uremia, extrarenal

uremia, etc., but a better name is urgently needed. As the most constant etiological factor appears to be diminution of the renal circulation, Maegraith and his associates have suggested the name renal anoxia. A similar syndrome with similar renal lesions is produced by temporary constriction of the renal artery. The renal anoxia has been attributed to arterial hypotension and vascular spasm. It must be borne in mind that experimentally the renal blood flow may vary independently of the general blood-pressure, so that the latter may be normal though the renal pressure has fallen to a dangerously low level.

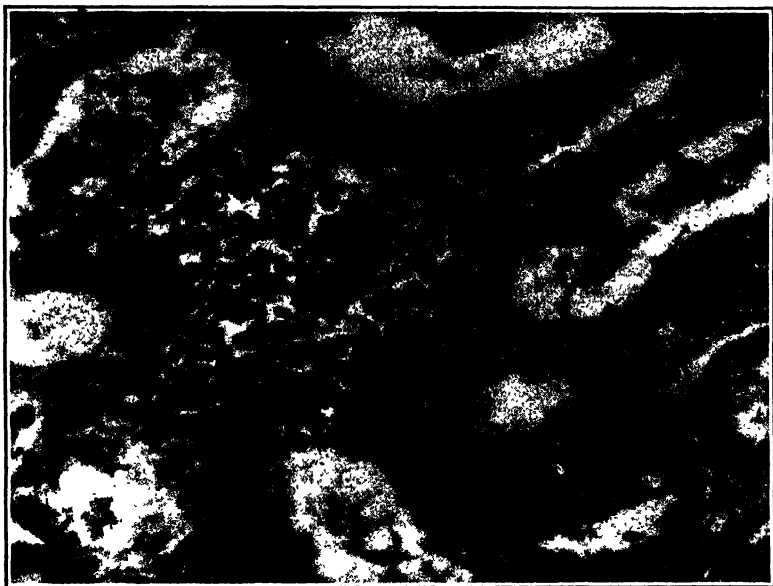


FIG. 304.—Sulphonamide nephritis. Note the focal interstitial nephritis and marked degeneration of tubular epithelium.  $\times 240$ .

Trueta and his associates in a series of beautiful experiments using both injection of dyes and radiographic technic have thrown entirely new light on the possible mechanism of production of renal anoxia. They have shown that a variety of noxious agents, acting apparently through the nervous system, may cause the blood to be diverted from the renal cortex and short-circuited through the medulla. The capacity of the vascular channels in the medulla is potentially large enough to transmit the entire renal inflow, thus rendering the cortex ischemic. In many of the conditions enumerated above there may be a renal defense mechanism whereby the cortex is spared exposure to toxins by means of this short-circuiting mechanism. If this is continued too long, permanent cortical damage results from anoxia. It may be that in conditions associated with decreased blood volume, such as hemorrhage and shock, the same mechanism may come into play to prevent further loss of fluid from the already reduced circulating blood volume.

The kidneys are enlarged, the cortex is pale and swollen and the medulla engorged. The chief lesions are in the ascending loop of Henle and the distal convoluted tubule. The epithelial cells of these tubules are degenerated and necrosed, and the lumen blocked by desquamated epithelial casts and debris stained by urinary pigments. The glomeruli are normal. The vessels of the medulla are greatly congested and there is hemorrhage into the tubules, so

that hematuria may occur. In the later stages the tubules are dilated and lined by a debased type of epithelium through which the fluid of the urine escapes back into the surrounding capillaries due to the osmotic pressure of the blood plasma, so that it is no longer free to enter the bladder.

**Mercuric Chloride Poisoning.**—

This is usually due to accidental or suicidal poisoning, sometimes to vaginal douching. Anuria rapidly develops, the nonprotein nitrogen in the blood rises, and death may occur from uremia. In some cases there is hypertension. If the patient does not die of uremia the anuria is followed by diuresis, the first urine being of low specific gravity. When death takes place after two or three days the kidneys present a picture of acute nephrosis. They are swollen and pale, there is extensive necrosis of the epithelium of the convoluted tubules, and the necrotic cells become detached and block the lumen of the tubules, thus accounting for the anuria. Acute calcification of the necrotic cells is not uncommon. (Fig. 305.) By the end of a week the tubules may be clear, yet the anuria persists. Apparently the glomerular filtrate escapes back through the bare walls of the tubules into the interstitial tissue, so that none of it reaches the bladder. This mechanism can be demonstrated in the kidney

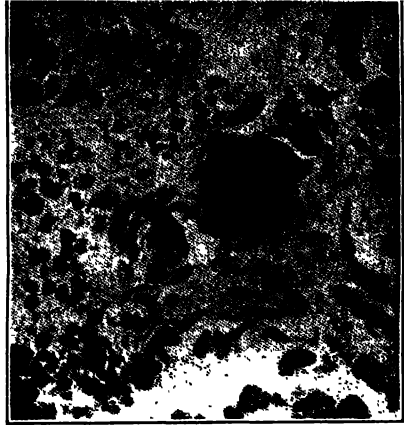


FIG. 305.—Corrosive sublimate poisoning. Acute calcification of the epithelium of the renal tubules. The two dark masses represent calcified cells.  $\times 300$ .

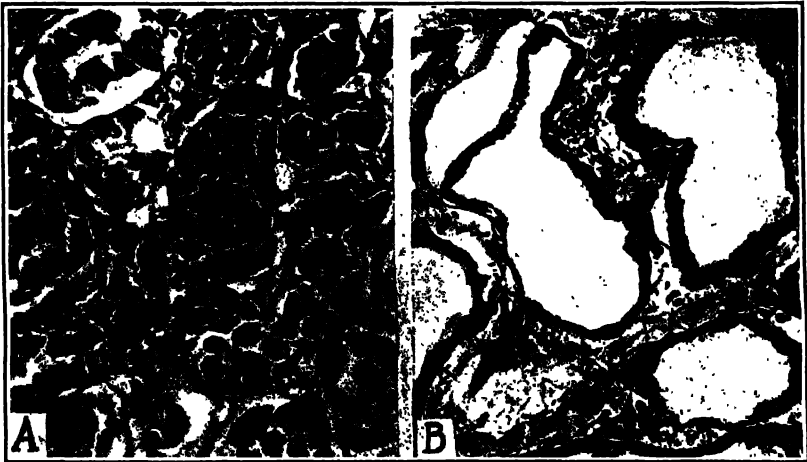


FIG. 306.—Mercuric chloride poisoning. A, early; B, late.  $\times 250$ .

of the frog poisoned with mercuric chloride (Richards). After the first week the tubules become relined with low, darkly-staining epithelium which is of little use for absorbing water and concentrating the urine. (Fig. 306.) The new epithelium gradually develops into a fully formed and functioning lining for the tubules.

**Renal Osteodystrophy.**—In this condition, known also as renal infantilism and renal dwarfism, there is an association of hypoplasia and fibrosis of the kidneys in children with defective growth and changes in the bones. In all cases there is dwarfism, and infantilism when the patient reaches puberty, but in only about two-thirds of the cases do the bone lesions develop. These lesions are osteoporosis, extensive deformities at the epiphyses, and bowing of the shafts. To these changes the name of *renal rickets* is often applied. They are supposed to be due to the renal insufficiency, which results in retention of phosphorus, upset of the calcium-phosphorus ratio, and acidosis. Decalcification occurs in the presence of acidosis and phosphorus retention. The essential defect is inability to excrete phosphorus. The blood may show marked lipemia and some nitrogen retention, but the blood calcium is said to be normal. Sometimes hypertension is present. The kidneys are contracted and fibrosed, and show marked arteriosclerosis. It is probable that the common cause of the contracted kidney is pyelonephritis in early childhood. It is possible, however, that in some cases the primary defect may be endocrine (parathyroid or pituitary) rather than renal in origin, in which case the renal lesions must be regarded as secondary. Price and Davie after weighing two views define the condition as “a disease of childhood characterized by skeletal demineralization with resultant deformities, and associated with chronic renal disease which in uncomplicated cases terminates in uremia.” The final result may be the same from whichever end one starts.

### OTHER FORMS OF NEPHRITIS

**Kidney in Bacterial Endocarditis.**—This condition has been known in the past as embolic glomerulonephritis, in the belief that the nephritic lesions were due to minute emboli from the vegetations of subacute bacterial endocarditis. This is not correct. It is true that the commonest lesions are infarcts, which present the usual appearance. Scattered over the surface there may be great numbers of small red spots, giving it the name of the “flea-bitten kidney.” These represent small hemorrhages into the glomerular spaces. The glomerular lesions may be diffuse or focal. The chief diffuse lesions are proliferation of the capillary endothelium, so that the tuft has a more cellular appearance than normal, and thickening of the capillary basement membrane. The focal lesions are less common, but are much more striking, and indeed are pathognomonic. The lesion takes the form of a patch of coagulation necrosis in the tuft which is readily recognized. (Fig. 307.) The lumen of the glomerular capillaries is filled with hyaline thrombi, similar to the material which blocks the vessels in acute glomerulonephritis (Bell).

The focal lesions are responsible for the hematuria which is so valuable a diagnostic feature in subacute bacterial endocarditis. Much more frequent, however, are widespread proliferative glomerular lesions mild in degree and involving both endothelial and epithelial cells. There may also be some hyaline thickening of the capillary loops. Apart from some albuminuria it is unlikely that these lesions produce any symptoms.

Hemorrhage takes place into the glomerular space owing to necrosis of the capillary loops, but the blood is more readily seen in the tubules than in the space, for it is washed out by the flow of urine. If the



necrotic part of the tuft comes in contact with the capsule there may be a localized proliferation of the capsular epithelium with the formation of a kind of epithelial crescent. Or adhesions may form between the tuft and capsule. If the patient lives long enough there will be healing and fibrosis.

The only symptom is the presence of red blood cells in the urine. As so few glomeruli are involved there is no danger of renal insufficiency. In the exceptional case which may die of uremia it will be found that a true diffuse glomerulonephritis has been added.

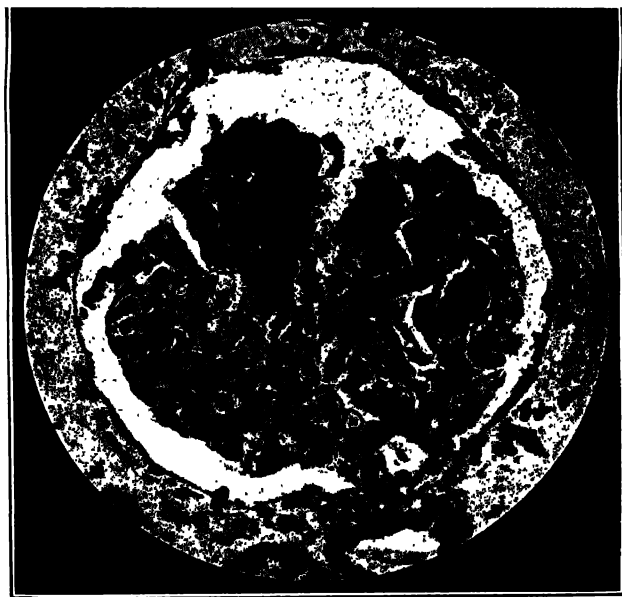


FIG. 307.—Glomerular lesion in subacute bacterial endocarditis. The upper part of the tuft is completely necrotic.  $\times 300$ .

**Focal Nephritis.**—The glomerulonephritis of Bright's disease is diffuse. There may also be a focal nephritis; (focal suppurative nephritis, *i. e.*, multiple embolic abscesses, is not considered here). The condition is usually called focal glomerulonephritis, but it differs so fundamentally from glomerulonephritis that it seems better to call it focal nephritis, thereby avoiding confusion. It complicates an acute infection, usually tonsillitis or streptococcal sore throat, sometimes pneumonia, typhoid or malarial fevers. At the height of the infection, not two weeks after the infection as in the glomerulonephritis of Bright's disease, the patient develops blood in the urine with albumin and numerous casts. As the infection subsides, the symptoms clear up. There is actual bacterial infection of the kidney, thus again differing from diffuse glomerulonephritis. The microorganisms can be found both in the urine and in sections of the kidney. Mild cases occur in which no definite focus of infection can be found, yet the patient suffers from recurring attacks of hematuria. It is probable that many cases of so-called "*essential hematuria*" are really examples of mild focal nephritis.

The *kidney* shows small hemorrhages on the surface, and on the cut surface

the glomeruli appear as red points. *Microscopically* the chief lesion is hemorrhage into the capsular space of many of the glomeruli. This explains the constant presence of blood in the urine. There may be small foci of inflammation in parts of the tuft, with some endothelial proliferation and accumulation of leucocytes. The tubules may show a little degeneration and contain blood. The great bulk of the parenchyma is untouched, so that there is no renal failure, no hypertension and no edema.

**Acute Interstitial Nephritis.**—This rare condition bears no relation to the other forms of nephritis. It occurs as a complication of the acute infectious fevers, especially scarlet fever and diphtheria. There is an acute inflammation of the interstitial tissue which is packed with lymphocytes, plasma cells, and a few polymorphonuclears. Yet the glomeruli and tubules remain intact. The inflammation is not diffuse, but is confined to definite areas. No bacteria are found in the lesions. Kimmelstiel believes that the condition represents an allergic reaction to foreign proteins rather than a bacterial infection. It can be produced by repeated injections of any non-bacterial protein such as serum or egg white, and is found in conditions associated with hemolysis, especially transfusion with incompatible blood. As the glomeruli and tubules are not invaded there is no renal insufficiency so that the cases seldom come to autopsy. The urine merely shows a little albumin and a few lymphocytes and red blood cells. It is of interest to note that in the dog interstitial nephritis is the most common form of renal disease, whereas glomerulonephritis and arteriolar nephrosclerosis practically never occur.

**Syphilitic Nephritis.**—This also is a rare form of nephritis. Acute secondary syphilitic nephritis usually occurs about the second month. It is explosive in character, corresponding with the acute manifestations in the skin and mucous membranes. The clinical picture is one of nephrosis, with marked edema and massive albuminuria. Doubly refractive bodies are common in the urine. The condition is rarely fatal. The effect of antisyphilitic treatment is dramatic, for the edema and massive albuminuria have been known to disappear in two days. The best test for the condition is the therapeutic test. The kidney shows marked tubular degeneration with spirochetes in the tubules. The glomeruli have not been examined carefully by modern methods.

Rich has described a peculiar type of lesion occurring in syphilitics, for the most part negroes, which he regards as syphilitic in origin, although no spirochetes can be demonstrated. The cut surface of the kidney presents glistening flecks like grains of sand. Microscopically there are dense collections of mononuclear cells in the interstitial tissue of the cortex, which form sharply defined nodules projecting into the lumen of the tubules and compressing them in a remarkable manner. The lumen of the tubules contains cholesterol crystals which are responsible for the glistening flecks seen with the naked eye.

## SUPPURATIVE INFECTIONS OF THE KIDNEY

Suppuration of the kidney is caused by the pyogenic bacteria, in particular *B. coli*, *Staphylococci* and *Streptococci*. Infection may be hematogenous or from below. Urinary stasis from whatever cause is liable to be followed by ascending infection from the bladder to the kidneys, probably by way of the lymphatics.

**The Pyemic Kidney.**—This is merely a renal manifestation of a general pyemia. Owing to a widespread blood infection pyemic abscesses are formed in various organs, including the kidneys. The infecting agent is usually *Staphylococcus aureus* or *Streptococcus hemolyticus*. The condition is a common complication of acute osteomyelitis, carbuncle, ulcerative endocarditis, and puerperal sepsis. When staphylococci are injected into the blood stream of a rabbit they

are arrested by the glomeruli and produce multiple small abscesses. Small yellow abscesses surrounded by a red zone are scattered over the surface and throughout the substance of both kidneys. (Fig. 308.) *Microscopically* they consist of circumscribed collections of polymorphonuclears, and often contain masses of cocci. The condition is a terminal one, and the patient dies of septicemia before there is time for any marked degree of renal destruction.

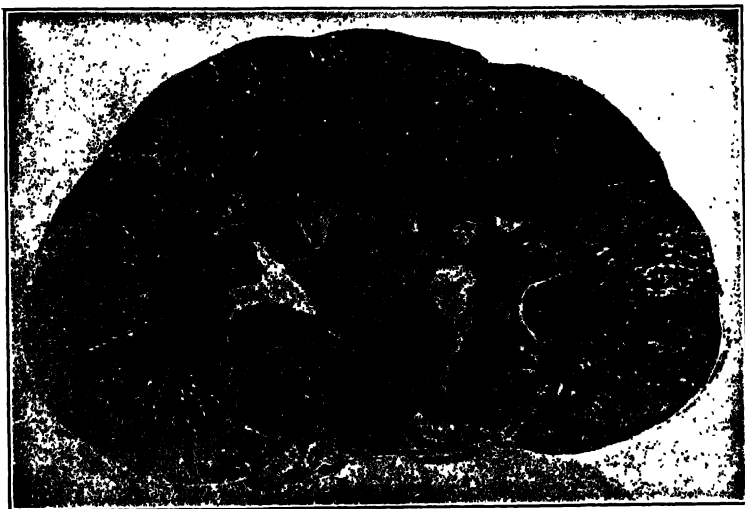


FIG. 308.—The pyemic kidney. Pyemic abscesses are scattered diffusely through both cortex and medulla.

**Pyelonephritis.**—Pyelonephritis is an interstitial inflammation of the kidney, and bacteria can be demonstrated in the tissues. This is in contrast to glomerulonephritis which is a disease of the nephrons in which no bacteria can be found. The term signifies inflammation of the kidney and renal pelvis. The renal infection may be hematogenous in origin, or it may ascend from below. An ascending infection is particularly common in infancy, pregnancy, and over the age of fifty due to prostatic enlargement in the male and cancer of the cervix in the female. In autopsy material the obstructive form is 12 times as common as the non-obstructive (Bell). Low obstruction (below the bladder) is more important than high obstruction (above the bladder). *Bacillus coli* is the common infecting organism, but the pyogenic cocci are frequent in hematogenous infections. The element of obstruction is of the greatest importance in determining the outcome. G. K. Mallory and his co-workers showed this by injecting colon bacilli intravenously into rabbits in which one ureter had been partially ligated; acute pyelonephritis developed in the obstructed kidney in 75 per cent of the animals, but never in the unobstructed kidney. Release of the obstruction after a few days induced healing of the

pyelonephritic process. In man the question of whether a blood infection will cause unilateral or bilateral renal lesions is probably largely dependent on the presence or absence of obstruction. In ascending infection some element of obstruction in the urinary tract is likely to be present from the beginning.

The *gross appearance* varies extremely with the stage of the disease. As a rule both kidneys are involved, but the lesions are often much less advanced in one than in the other. They may be focal or diffuse. In the acute stage the kidney is swollen and congested, and the pelvis is of a bright red color and filled with pus. Under the capsule there are numerous yellow spots representing areas of suppuration, as well as dark irregular patches which form the base of wedge-shaped areas in the renal substance. The superficial lesions are often raised above the surface as small pustules. If healing occurs later they are represented by depressed U-shaped scars. The cut surface shows patchy areas of suppuration which tend to be spherical in the cortex and linear in the pyramids. If suppuration is progressive, abscess cavities are formed with gradual destruction of renal tissue. The outline of the calyces is destroyed, and the resulting distortion seen in the x-ray film is an important feature in the clinical diagnosis. When obstruction is marked from the beginning the element of hydronephrosis enters the picture, hydronephrotic atrophy leading to destruction of the medulla and much of the cortex. The kidney becomes converted into a bag of pus, a condition known as *pyonephrosis*. A pure hydronephrosis in an advanced stage may become infected. Such a kidney is much enlarged, the surface is irregularly lobulated, and when it is opened it presents a picture of pyonephrosis in which a mere shell of kidney tissue is left.

The disease may develop in a more gradual and insidious manner with little frank suppuration. The inflammation, which is chronic in character, extends here and there in the kidney, destroying renal tissue, but being followed later by healing, fibrosis, and contraction. The result is a contracted kidney, on the surface of which there are depressed scars. If these scars are of considerable size they are apt to be regarded as healed infarcts. When they are much smaller the effect is to give the kidney a granular appearance which may be hard to distinguish from that of chronic glomerulonephritis or arteriolar nephrosclerosis. This condition is called *pyelonephritic contracted kidney*, and in the past it has frequently been mistaken for the two diseases just mentioned. Chronic and healed pyelonephritis is a much commoner condition than used to be supposed. Weiss and Parker in their classic paper find it to be a more frequent cause of contracted kidney than glomerulonephritis. The surface of the kidney is finely granular in glomerulonephritis, more coarsely scarred in chronic pyelonephritis. The scars of nephrosclerosis are pale and on the cut surface are V-shaped like those of healed infarcts. The scars of pyelonephritis tend to be dark (due to vascularity) and saddle-shaped on the outer surface and U-shaped on the cut surface. In distinguishing

between chronic pyelonephritis and other conditions with which it may be confused, attention should be paid to the renal pelvis (thickened), calyces, and ureter.

The *microscopic picture* varies with the stage as much as does the gross appearance. There may be many small abscesses and widespread interstitial infiltration with polymorphonuclear leucocytes. Much more usual, however, is a streaky linear round-cell infiltration with an admixture of polymorphonuclears. (Fig. 309.) In both cases there is destruction of the renal tubules, with gradual replacement by scar tissue which is more abundant and dense than in nephrosclerosis. Many tubules are filled with pus cells. The process is characteristically patchy, and in the chronic cases the tubules in the intervening areas are either normal or dilated. A striking feature, especially in the scarred areas, is the presence of dilated tubules lined by flattened epithelium, and filled with dense, acidophilic colloid-like material, so that in places the tissue may resemble the thyroid gland. These so-called colloid casts tend to be somewhat denser than the casts seen in glomerulonephritis and nephrosclerosis, but have no distinctive staining reactions. The experimental studies of Mallory suggest that the colloid material may possibly be derived from the nuclear débris of polymorphonuclear leucocytes. The glomeruli may be intact, but in the scarred areas they may be completely hyalinized. Reference has already been made (page 626) to the focal proliferative glomerulitis which may be found in chronic pyelonephritis with marked destruction of renal parenchyma. Periglomerular fibrosis is a marked feature even when the glomeruli are intact. In the renal pelvis there is round-cell infiltration or fibrosis, a valuable diagnostic feature for the pathologist in quiescent cases. The arteries in the affected areas show endarteritis obliterans, such as may occur in any area of chronic inflammation. Much of the arterial thickening represents disuse atrophy; it is an adjustment of the lumen to the decreased blood flow.

The *clinical picture* will naturally depend on the stage of the disease. In acute cases there is pain and tenderness over the kidneys, fever,

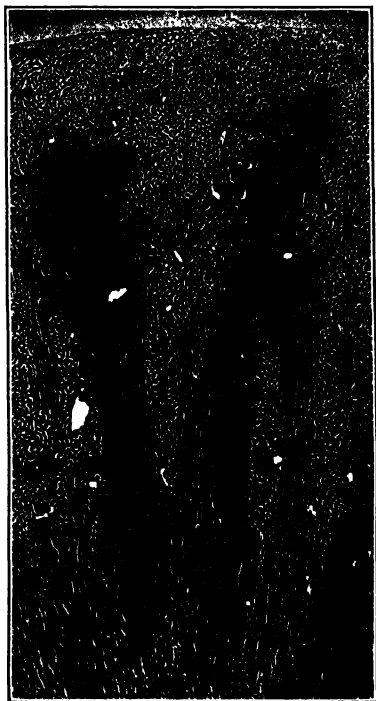


FIG. 309.—Pyelonephritis. The linear circumscribed lesions involve both cortex and medulla.

leucocytes and pyuria. In chronic cases with extensive scarring the symptoms will be those of contracted kidney due to other causes, those, namely, of renal failure with or without hypertension. The hypertension is presumably due to renal ischemia, but the matter is not quite so simple as it seems, for of two patients with equally ischemic kidneys one may have marked hypertension whilst in the other the blood-pressure is normal. In the pyelonephritis which is so common after the age of fifty hypertension is a frequent accompaniment, but as both conditions are common at this period the element of coincidence cannot be eliminated. In the pyelonephritis of childhood, the late stage of which was first recognized by Longcope, this element does not need to be considered. In some of these cases hypertension has developed a number of years after the onset of the disease. As chronic pyelonephritis may initiate hypertension, and as the disease is sometimes unilateral, the tempting possibility presents itself of removing the offending kidney and relieving the hypertension. A number of cases have been published in which permanent relief has been afforded, but it is probable that for every recorded success there are ten or twenty failures of which nothing is heard. The success of an occasional operative case proves nothing.

**Perinephritic Abscess.**—This condition, also called perirenal abscess, is a localized suppuration in the perirenal tissue, usually due to *Staphylococcus aureus* from a boil or carbuncle in the skin. Occasionally a pyelonephritis or a small localized focus of suppuration in the kidney is the evident source of infection, but in most cases the perirenal lesion has the appearance of being primary. As the result of experimental work on hematogenous infection in animals it is known that staphylococci may produce a minute lesion in the renal cortex, and then pass along cortical lymphatics through the capsule to the perirenal tissue. This is what probably happens in man, and an abscess is produced, usually behind the kidney.

A *carbuncle of the kidney* is also a localized hematogenous staphylococcal infection. A large necrotic area containing several foci of suppuration is separated from the rest of the kidney by a broad zone of granulation tissue. Ball and Evans' book contains a beautiful picture of the lesion. A remarkable feature is the relative freedom of the urine from pus. This may be explained by the destruction of the tubules in the lesion itself, and the intact condition of the glomerulo-tubular units at the periphery.

### TUBERCULOSIS OF THE KIDNEY

Tuberculosis of kidney occurs in two forms: (1) acute miliary tuberculosis, and (2) chronic tuberculosis. *Miliary tuberculosis* is merely part of a general miliary infection, and is a postmortem finding. The kidney is studded with miliary tubercles, which on the surface may be mistaken for the abscesses of a pyemic kidney, but they show no border of congestion.

*Chronic tuberculosis*, also known as *ulcero-caseous tuberculosis* and *surgical tuberculosis*, is at first a local condition. The primary lesion is often in bone. The bacilli are carried to the kidney by the blood. It used to be believed that tubercle bacilli could be excreted by healthy kidneys (*excretory bacilluria*). This is wrong. A lesion is always

present in the kidney, although serial sections may be needed to demonstrate it. Band points out that the earliest lesions occur in the cortex in relation to the glomeruli, although they may only be seen in microscopic sections (he examined 2,000 sections from each half kidney). These minute primary lesions often heal. They may ulcerate into the tubules, and as the collecting tubules converge at the apex of the pyramids it is natural that secondary lesions should develop there. These are the first lesions which are readily visible to the naked eye. Ulceration of the calyces now occurs, and in the x-ray picture (pyelogram) a characteristic distortion of the outline of the calyces and pelvis can be detected, which may allow a remarkably early diagnosis to be made.



FIG. 310. —Tuberculous pyonephrosis. In the cortex of the lower part there are solid caseous areas; further up cavity formation has taken place; the ureter is considerably thickened.



FIG. 311.—Renal tuberculosis.  $\times 100$ .

The lesion at the apex of the pyramid is at first a localized nodule, but infection spreads up the lymphatics along the line of the collecting tubules, as well as down into the pelvis. In this way a *tuberculous pyelonephritis* is produced. In the tuberculous form there is a much greater tendency to destruction (*renal phthisis*), and large cavities with rough ragged walls are produced containing thick creamy odorless pus which is sterile on culture unless secondary infection has occurred. These communicate with the pelvis, so that a large amount of pus appears in the urine. The condition is now a *tuberculous pyonephrosis*. (Fig. 310.) Caseation, softening, and liquefaction may eventually lead to destruction of the entire kidney. The kidney may be con-

siderably enlarged or may become shrunken. Much depends on whether tuberculous stricture of the ureter occurs. Such a stricture may prevent the pus from reaching the bladder, and thus mask the true nature of the condition. In the shrunken kidney the pus becomes inspissated and converted into a putty-like material in which lime salts may be deposited. In the roentgenogram these deposits may give an outline of the calcareo-caseous sac representing the kidney or merely spotty shadows. The *microscopic appearance* is that of tuberculosis in its various stages. (Fig. 311.)

**Spread.**—The spread of the disease is of great importance. At first localized, the infection spreads very readily in the connective tissue of the submucosa of the renal pelvis. It is true that in experimental tuberculosis of the kidney healing may occur, but when renal phthisis has developed, spontaneous healing can no longer be hoped for, and this is the stage at which a diagnosis is likely to be made. Infection spreads to the *ureter* with the formation of tubercles and tuberculous granulation tissue in the mucosa and ulceration of the surface. The chief lesions are in the upper and lower thirds. A stricture may develop, but more often the ureter is converted into a rigid, thickened, dilated tube. The *bladder* is infected early, and the chief symptoms—pain and frequency of micturition—are due to this infection. It begins at the opening of the ureter, where hyperemia and tubercles can be seen with the cystoscope and an early diagnosis established in this way. The infection spreads along the submucosa of the trigone, causing ulceration of the overlying mucous membrane. It may extend to the prostate and seminal vesicles, and along the vas deferens to the epididymis, thus producing a *genito-urinary tuberculosis*. There is a remarkable tendency for the bladder lesions to heal, and removal of the kidney may be followed by complete recovery. The *other kidney* becomes infected sooner or later, so that at autopsy the condition is always bilateral, though much more marked on one side than the other. This involvement is probably due to an ascending infection from the bladder.

The *urine* often contains blood in the early stages, owing to destruction of small vessels in the renal papillæ. Pus is a later development, depending on the amount of caseation and liquefaction. It is seldom as abundant as in pyelonephritis and pyonephrosis. Tubercle bacilli may be found with the microscope, or if very few are present, culture or guinea-pig inoculation may be necessary.

**The Relation of Symptoms to Lesions.**—The two chief symptoms are frequency of micturition and blood in the urine. These are early as well as common symptoms. The frequency is vesical and the hematuria renal in origin. The *frequency*, which is often associated with pain on urination, is due to lesions in the sensitive trigone of the bladder. It becomes more marked as the capacity of the bladder diminishes. There is often an associated *polyuria*. Renal pain is not an early or a prominent symptom, although there may be an aching in the loin aggravated by jolting. *Renal colic* may be caused by the release of blood along the ureter. The *hematuria* is caused by destruction of vessels in the renal calyces. *Pus in the urine* is a later devel-



opment, depending on the amount of caseation and liquefaction. It is seldom as abundant as in pyelonephritis and pyonephrosis. Tubercle bacilli may be found with the microscope, or culture and guinea-pig inoculation may be necessary. There are usually no ordinary pyogenic bacteria. Death is usually due to uremia from renal failure, sometimes to general miliary tuberculosis.

### CYSTS OF THE KIDNEY

**Polycystic Kidney. Congenital Cystic Kidney.**—This condition is found once in every 500 autopsies (Bell). It is nearly always bilateral, but in about 5 per cent of cases may be unilateral. There are two periods of life at which it is found. About 30 per cent occur in infants, the majority still-born. The remaining cases present symptoms in early adult and middle life. The progressive atrophy of the parenchyma caused by continuous dilatation of the cysts is balanced during youth by compensatory hypertrophy, but by the third decade this compensatory power is lost. The kidneys may be enormously enlarged or only slightly so. They are converted into a series of cysts, which may occasionally communicate with one another but never with the renal pelvis. (Fig. 312.) The surface is grossly nodular owing to the



FIG. 312.—Polycystic kidney. The kidney is enlarged and converted into a series of cysts containing thick material which has been coagulated by the fixative.

large cysts. The contents may be thin or thick and viscid, clear amber or dark brown from hemorrhage, and sometimes contain urea. Hardly any renal tissue may be left, so that the occurrence of hypertension, renal insufficiency, and uremia is easily understood. Infection of the cysts is not uncommon. *Microscopically* the cysts are lined by cubical epithelium, but in the large cysts it may be flattened. The remaining kidney tissue shows marked evidence of nephrosclerosis, with fibrosis of the glomeruli and disappearance of the tubules. Ritter and Baehr point out that gross study of injected kidneys shows that the interlobar and interlobular arteries lie mainly in the cyst walls, often just under the lining epithelium. These vessels are easily ruptured as the result of hypertension or slight trauma, so that the

cysts frequently contain fresh or old blood, and the patient suffers from attacks of lumbar pain. If the hemorrhage into a cyst should cause rupture into one of the calyces there will be hematuria—a not uncommon symptom. When the kidney is injected with an opaque substance and roentgen-rayed, there is found to be a great disappearance of vessels and occlusion of the arterial tree.

The congenital nature of the condition is suggested by the occasional occurrence of other congenital anomalies. Small cysts are sometimes present in the liver (due to malformation of the bile ducts), and more rarely in the pancreas. There is moreover a strong hereditary tendency. It used to be supposed that the cysts were due to failure of the



FIG. 313.—Large solitary cyst of the kidney.

convoluted tubules to fuse with the collecting ones, but it is more probable, as Kampmeier points out, that the cystic condition is merely a persistence of one stage of renal development. In the early embryo the convoluted tubules which first develop in connection with the collecting tubules are not permanent, but become detached and persist for a time as cystic structures. Normally these fetal cysts atrophy. If they persist they form a cystic kidney. Clinically it is justifiable to speak of a surgical and a medical type (but not with respect to treatment). In the surgical type the symptoms such as pain, tumor, and hematuria, are referable to one kidney. In the medical type there are symptoms of acute or chronic renal insufficiency, with arterial hypertension in over 50 per cent of the cases.

**Solitary Cyst.**—Sometimes a large single cyst is found projecting from one pole of the kidney, which may cause a degree of enlargement that can be detected clinically. (Fig. 313.) Some of these cysts may attain a very large size. There may be more than one of these “solitary” cysts. Often the cyst is quite small. The contents are serous and rarely contain urea. Hemorrhage may occur into the cyst. The condition is most probably congenital.

## TUMORS OF THE KIDNEY

There is no more perplexing chapter in the whole of pathology than that which deals with tumors of the kidney. Endless varieties have been described, but nearly all the malignant tumors of the kidney appear to be variants of two main types, and these alone will be considered here. For details of the variations the reader is referred to Ewing's great treatise on tumors. The main types are the hypernephroma (Grawitz's tumor) and the embryoma (Wilms' tumor).

**Hypernephroma.**—This tumor owes its common name to the original suggestion of Grawitz, in 1883, that it was derived from rests or remnants of adrenal cortex which had been included in the kidney. For long this was the popular view, but it must be given up, for there is no doubt that the tumor is a renal carcinoma arising either from adult tubercles, or, as suggested by Wilson in 1910, from islets of nephrogenic tissue which have persisted in the renal cortex, thus bringing it into line with the embryoma (see below). Such developmental rests are common in infants though rare in adults, thus illustrating the general law of tumor growth that persisting undeveloped embryonic tissue diminishes as age increases, but the incidence of malignant tumors derived from it increases. As the old name is based on a wrong theory it should really be given up, but it is so firmly entrenched that it is almost impossible to uproot it. The chief argument in favor of the original Grawitz view is that the tumor is often composed of clear, vacuolated, lipid-filled cells similar to those of the adrenal cortex, but similar clear cells are found in adenomas of the kidney composed of typical tubules. The hypernephroma may show a tubular formation which is never seen in the adrenal gland or tumors of the adrenal cortex. The latter tumors are associated with sex disturbances (virilism) which are constantly absent in hypernephroma.

The *gross appearance* is so characteristic that it can usually be recognized at a glance. (Fig. 314.) The tumor forms a rounded mass usually in the upper or lower pole, which may attain a large size. At first it appears encapsulated, but later is invasive. The great characteristic of the cut surface is its variegated appearance. Yellow is the chief color (due to lipid), but there are also red hemorrhagic areas and cysts of varying size, while only a small piece of normal kidney tissue may be left. Some of the cysts contain serous or mucinous fluid, but others represents areas of necrosis into which hemorrhage has occurred. There may be a fibrous core in the center of the tumor.

The *microscopic picture* may be as varied as the gross appearance. The tumor cells are usually very characteristic, being large and rounded with a peculiarly clear or vacuolated cytoplasm. (Fig. 315.)



FIG. 314.—Hypernephroma. The cut surface has a variegated appearance.

The clearness or vacuolation is due to the presence of a large amount of lipid (mostly cholesterol ester), and in part to the presence of glycogen, shown by Best's carmine stain after alcohol fixation. Occasionally the tumor is composed of dark granular cells; this granular-cell form is much more malignant. The arrangement of the cells is also variable. There are three possibilities, which in their order of frequency are: (1) a cystic papillary formation, in which papillary processes project into indefinite cystic spaces, but with no real tubular formation; (2) an alveolar arrangement of solid cords, divided into masses by thin septa; (3) occasionally a definitely tubular arrangement

which irresistibly suggests that the tumor is of renal origin. The stroma is scanty, but the bloodvessels form a striking feature of the picture; they are usually numerous and very large, and the vessel wall



FIG. 315.—Microscopic appearance of a hypernephroma. The clear cells show a very marked alveolar arrangement.  $\times 200$ .

often seems to be formed of tumor cells, thus accounting for the frequent hemorrhage into the tumor and the tendency to metastasize by the blood stream.

**Spread.**—The tumor may remain silent for a long time, and metastases are often the first evidence of a renal tumor. At first the tumor is sharply separated from the kidney by a fibrous capsule, but sooner or later the malignant character becomes obvious, the capsule gives way, and the kidney is invaded. There is a special tendency to invasion of veins, and the tumor may grow into the renal vein and even into the inferior vena cava, with widespread metastases as the result. The lungs and bones are involved most often, but the liver often shows metastases, and the regional lymph nodes are invaded *via* the lymphatics. In the lungs the metastases show a curiously clear-cut outline in the roentgen-ray picture known as the "cannon-ball" appearance. Hypernephroma is one of the most important causes of secondary tumors of bone, and the first manifestation that there is anything wrong with the patient may be the occurrence of a spontaneous fracture. A curious feature is that in 60 per cent of the cases there is a solitary bone metastasis. The order of frequency of involvement is upper end of humerus, spine, femur, pelvis, and ribs.

**The Relation of Symptoms to Lesions.**—Of the symptoms painless hematuria is by far the most important, and it occurs fairly early in over 50 per cent of the cases. It is accounted for by the numerous large thin-walled blood spaces, which readily rupture into the renal tubules. Pain is uncommon, and a tumor can be felt only late in the disease. The tumor causes deformity of one or more of the calyces of the renal pelvis at an early stage, and this may be detected in a pyelogram. Long-continued fever is a remarkable feature of some cases; it is probably a protein fever due to breaking-down of tissue. A pyelogram (roentgen-ray of pelvis) shows the following: (1) spider distortion due to stretching of the calyces, (2) filling defects in the pelvis, (3) displacement of the ureter outwards. In embryoma, on the other hand, the pyelogram shadow is displaced by the tumor but not otherwise altered until late, when the renal pelvis is invaded. The *prognosis* is bad owing to the tendency to bloodspread, but early removal may be followed by cure.

**Embryoma, Wilms' Tumor.**—This is the commonest abdominal malignant tumor of early childhood. It usually occurs during the first three years of life and after the age of five years it is infrequent, but it may very rarely occur in adults. It may attain an enormous size, nearly filling the abdomen. Quite frequently it is bilateral. The diagnosis cannot be made until a tumor appears, for there is no hematuria and no pain, because the renal pelvis is not invaded. Intravenous urography may show a complete absence of the normal roentgenogram shadow or distortion of the calyces. Fever occurs in 50 per cent of the cases. There is a marked response in the size of the tumor to radiation, a useful diagnostic point.

The tumor, which commences in the cortex, is gray, soft, and has the homogeneous character of a sarcoma (Fig. 316), but necrosis and hemorrhage may alter this appearance. It tends to destroy the whole kidney, and may spread to neighboring organs, but distant metas-

tases by the blood stream are not frequent. In this respect it differs completely from hypernephroma. The *microscopic appearance* varies in different cases and in different parts of the same tumor. The general character is sarcomatous, and in the past the Wilms' tumor has been classed as "sarcoma of the kidney in children." The cells may be round or fusiform. Glandular (tubular) elements are often present, and such tumors have often been called *adenosarcoma*. (Fig. 317.) Smooth muscle and striated muscle are not uncommon, and in rare cases there may be cartilage and bone. The tumor is markedly radio-sensitive.



FIG. 316.—Embryoma. The homogeneous appearance of the cut surface is in striking contrast to the variegated surface of hypernephroma. The kidney is at the right of the tumor.

The Wilms' tumor is a developmental tumor, and is best called an embryoma or an embryonal mixed tumor. It may seem strange that an epithelial organ such as the kidney should give rise to a developmental tumor with connective-tissue (sarcomatous) characteristics. This is readily explained by recalling that the epithelium of the urinary tract

is derived from mesoderm (intermediate cell mass); the convoluted tubules develop from undifferentiated mesenchyma which has the appearance of cellular connective tissue in which glandular

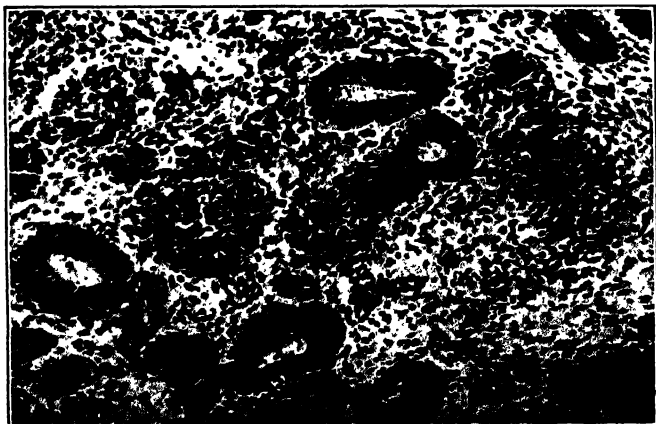


FIG. 317.—Wilms' tumor, showing a combined carcinomatous and sarcomatous appearance.  $\times 150$ .

structures are formed. This is exactly the appearance presented by the usual form of Wilms' tumor. The occasional formation of muscle and cartilage is a perversion of growth on the part of the embryonic mesenchymal cells.

**Other Tumors.**—*Fibroma* occurs fairly often as a small circumscribed nodule in a pyramid or papilla. Narrow tubules are usually scattered through the fibrous tissue. The lesion is rather a *hamartoma* than a true tumor, *i. e.*, a developmental defect in tissue combination (*hamartia*, defect) with a limited capacity for aberrant growth. *Adenoma* forms a similar nodule in the cortex. It consists of tubules, sometimes lined by the same clear type of cell that is so characteristic of hypernephroma, and thus providing additional evidence for the tubular origin of that tumor. There may be cyst formation with papillary processes, such a tumor being really a *papillary cystadenoma*. *Lipoma* and *sarcoma* are rare tumors: most sarcomas develop from the capsule and invade the cortex secondarily. *Villous papilloma* of the pelvis is described in another section.

### CIRCULATORY DISTURBANCES OF THE KIDNEY

**Chronic Venous Congestion.**—The congestion is due to the ordinary causes, *i. e.*, cardiac disease, and obstruction in the pulmonary circulation from emphysema, etc. The entire kidney is congested, but particularly the pyramids which are very dark. It is much firmer than normal, a condition known as *cyanotic induration*, and due partly to the increased blood content, partly to thickening of the capillary walls, but not to any increase in the interstitial tissue. The glomerular capillaries are greatly dilated and engorged with blood, and there may be red cells in the capsular space owing to rupture of the distended capillaries. In this condition, known clinically as *stasis kidney* and *cardiac kidney*, the urine may be diminished in amount, and may contain albumin and sometimes red blood cells. The dye excretion may fall low, but the concentrating power remains normal. Under treatment directed to the heart the condition of the urine may rapidly clear up.

**Infarction.**—The kidney is one of the commonest sites of infarcts. The cause of the vascular obstruction is usually arterial embolism, but it may be due to thrombosis of the small arteries. The infarct shows the usual characters which are described in Chapter III. The necrotic area is surrounded by a zone of congestion, which in the earlier stages of the process may show much hemorrhage. For this reason there may be red cells in the urine at this stage. On the other hand, the urine is often normal. A renal infarct is usually without symptoms, there may be pain and tenderness over the kidney, and in exceptional cases the condition may simulate perforation of a viscus.

**Symmetrical Necrosis of Renal Cortex.**—This fortunately rare and fatal condition is marked by anuria at the outset, and runs a clinical course similar to that produced by extirpation of both kidneys. It is twice as common in pregnancy (late stage) as in the non-pregnant state, occurring in both sexes and at any age. It is in essence a massive ischemic cortical infarction including the columns of Bertin. This massive lesion is the result of the coalescence of innumerable small infarcts. The gross picture is so characteristic that it can

be recognized at a glance. Almost the entire cortex, with the exception of a very thin surface layer supplied by the capsular arteries, is a bright yellow outlined with red. A similar appearance is seen in the massive necrosis produced by the so-called elixir of sulphanilamide in which the solvent was di-ethylene glycol. The lesion is an ischemic necrosis due to thrombosis of large numbers of small arteries and arterioles. The walls of these vessels are necrotic. The primary lesion appears to be in the arterial wall, and it is probable that it is of the nature of an allergic reaction in this tissue (Duff and More), a view which would explain the suddenness of onset. Similar small necrotic and arterial lesions are occasionally found in the adrenals, spleen and bowel. For further details regarding this remarkable condition the review by Duff and More should be consulted.

**Orthostatic Albuminuria.**—What has been called benign albuminuria is of common occurrence in children and young adults, and is due, certainly in many cases, to a circulatory disturbance of the kidney. The distinguishing feature of the albuminuria is that it is absent when the person is lying down and appears when he assumes the erect posture. For this reason it is called orthostatic or postural albuminuria. The albumin is most marked in a specimen passed after the person has been up for some little time in the morning. It is commonly associated with marked lordosis of the lumbar spine (Jehle). When this lordosis is corrected, as by the child putting his foot on a stool, the albuminuria disappears even though the erect position is maintained. The vena cava lies to the right of the mid-line, so that the left renal vein has to cross the vertebral column, and is liable to be compressed if lordosis is at all marked. When catheters are placed in the ureters of a person who suffers from this condition, it will be found that when he assumes the erect (and lordotic) position the urine coming from the left ureter will contain albumin, while that coming from the right is normal (Sonne). There may be anuria for one-half hour on the part of the ischemic left kidney, while the right kidney continues to secrete normal urine. The condition is an anomaly, but can hardly be called pathological. It tends to disappear as the person grows up and the lordosis lessens. The prognosis is excellent.

**Hematuria.**—This subject may be considered in connection with circulatory disturbances, although it is usually due to quite different causes. Blood in the urine may come from the urethra, bladder or kidney. Only the renal causes are considered here. In some cases the blood can be seen with the naked eye; in others it can only be seen with the microscope. In the latter group it is better to speak of red cells rather than blood in the urine. (1) The hematuria may be due to *circulatory disturbances, e. g.,* chronic venous congestion, infarction. (2) *Inflammatory and necrotic conditions, e. g.,* acute glomerulonephritis, embolic glomerulonephritis, focal nephritis, malignant nephrosclerosis. (3) *Tuberculosis* of the kidney. (4) *Tumors.* The common cause is hypernephroma, but papilloma or carcinoma of the renal pelvis may occasionally cause bleeding. (5) *Renal calculus,* the stone either remaining in the pelvis or passing down along the ureter. (6) *Essential hematuria* is a condition in which there is hemorrhage, sometimes severe, from one kidney, but when the condition is removed no cause is found. In most cases there is probably a focal nephritis which has been overlooked, or a varicosity in one of the renal papillæ.

## DEGENERATIONS OF THE KIDNEY

**Tubular Degeneration.**—This is not an entity but a convenient term to cover a diversity of conditions. *Cloudy swelling* is the commonest of all kidney lesions. It may occur in any febrile or infectious disease. Postmortem changes mimic it closely, and it is often difficult to know how much of the change is antemortem, how much postmortem, unless the material is very fresh. It has already been described in Chapter II.



All grades of severity of this albuminous degeneration may occur. The changes are most marked in the convoluted tubules. They may be classed as *nephroses*, but this is a dangerous term. It is safe enough when used in a strictly pathological sense, but it is apt to be seized by the clinician and perverted to his own uses. A large number of chemical poisons may be used experimentally to produce tubular degeneration or nephrosis, *viz.*, uranium nitrate, potassium bichromate, phosphorus, arsenic, and mercuric chloride. The last-named is the only one of clinical importance, for corrosive sublimate is often used for suicidal purposes (see page 633).

**Fatty Degeneration.**—Two forms may be recognized, the diffuse and the patchy. The *diffuse form* affects the entire parenchyma, especially the convoluted tubules. It is caused by pernicious and other anemias, diabetes, bacterial toxins, phosphorus, chloroform, etc. The condition is described in Chapter III. The fat globules in the cells consist of neutral fat (glycerol esters). The *patchy form* is seen in the degenerated tubules of Bright's disease (glomerulonephritis, nephrosis, nephrosclerosis), and in amyloid degeneration. Owing to the irregular distribution the yellow fat gives the cortex a mottled or speckled appearance. Some of the fat is in the neutral form, but much of it is cholesterol ester. This lipid is present not only in the epithelial cells of the tubules but also in the interstitial tissue. Its nature can be recognized by the fact that it is anisotropic (doubly refractive) under crossed Nicol's prisms.

**Amyloid Degeneration.**—The general pathology of amyloid disease is discussed in Chapter III. It is a complication of a suppurative, tuberculous, or syphilitic lesion, but occasionally no evident cause can be found even at autopsy. The kidney is large and pale, and may closely resemble the "large white kidney" of subacute glomerulonephritis or nephrosis. But it is of firm consistence, and the cut surface has the characteristic translucent or waxy appearance of amyloid organs. When the iodine test is used the affected glomeruli stand out as dark-brown dots on the cut surface. If the progress of the disease is slow and the patient does not die of the original suppurative lesion, the kidneys may become contracted and granular.

*Microscopically* the amyloid is deposited in three situations: the glomeruli, the arterioles, and around the collecting tubules. It is a connective-tissue change, the epithelial changes being entirely secondary. The most striking lesions are in the glomeruli. (Fig. 318.) The deposit of amyloid occurs between the basement membrane of the loop and the endothelium, so that the capillary loops are gradually closed. Some of the loops remain open for a long time, and through these damaged loops large quantities of albumin escape into the urine. In time the glomeruli are converted into large bloodless structureless masses of amyloid. When the glomerulus is occluded the corresponding tubule undergoes atrophy and is replaced by fibrous tissue. In this way marked tubular atrophy, fibrosis, and shrinking of the kidney may occur. In the earlier stages the tubules show

marked evidence of degeneration, and the epithelium is filled with fatty and hyaline droplets and may contain cholesterol ester. Large homogeneous casts are formed in the tubules, and in the urine they are known as "colloid" casts. Much of the atrophy of the parenchyma is due not only to ischemia from glomerular atrophy but to pressure from the amyloid which gradually accumulates in the arteries and in the connective tissue around the tubules.



FIG. 318.—Amyloid disease of the kidney. The glomerulus is greatly enlarged by the amyloid, but the presence of blood cells (black) shows that the circulation is still going on.  $\times 275$ .

The *symptoms* are nephrotic in type, *i. e.*, massive albuminuria and edema, but if the patient lives long enough he may die of uremia with high non-protein nitrogen in the blood and hypertension. The nephrotic symptoms are based on hyperpermeable and still patent glomerular capillaries, whilst the terminal nephritic picture is that of the contracted ischemic kidney. Amyloid disease may last for many years. If the underlying cause can be arrested, as in syphilis, the amyloid disease may also cease to progress and even retrogress. Experimental evidence shows that amyloid material may become absorbed, and perhaps this may occur in man.

**Deposits of Pigment.**—*Blood pigment* may accumulate in the cells of the convoluted tubules when there is much blood destruction and the hemoglobin passes through the glomeruli and is concentrated in the tubules. This is well seen in pernicious anemia and paroxysmal hemoglobinuria. The granules of hemosiderin give the Prussian blue reaction for iron. Casts of hematin granules are seen in the tubules as the result of hemoglobin-

uria from unsuitable blood transfusion. *Bile pigment* may accumulate as fine granules in the cells of the convoluted tubules in persistent jaundice. In severe cases of jaundice of the new-born the pigment may be deposited in the apices of the pyramids, a condition known as *bilirubin infarcts*. A much commoner condition seen in new-born children is *uric acid infarcts*. They take the form of yellow streaks at the apices of the pyramids, and consist of deposits of urates in the collecting tubules. It is probable that they soon disappear. When melanin is excreted it appears in the cells of the loop of Henle.

*Glycogen deposits* occur in von Gierke's disease and also in severe cases of diabetes mellitus, although they are more rarely seen since the introduction of insulin. In diabetes the cells chiefly affected are those lining the loop of Henle. The affected cells are large and perfectly clear owing to the glycogen being dissolved out, so that the tubule has a very striking and characteristic appearance. It is probable that the glycogen is derived from the sugar in the urine.

**ATROPHY AND HYPERTROPHY OF THE KIDNEY**

*Atrophy* of the kidney may occur to a slight degree in general conditions of atrophy such as old age, but the only cause of real importance is loss of the blood supply. This may be caused by arteriosclerosis, which may affect the larger branches of the renal artery (senile contracted kidney) or the arterioles (primary contracted kidney). Glomerular ischemia, the result of glomerulonephritis, leads to disappearance of the tubules and shrinking of the kidney (secondary contracted kidney). Sometimes one part of the kidney may be very atrophic, the remainder only partially so. There may be congenital hypoplasia. Pressure atrophy is typically seen in hydronephrosis, where the constant pressure of retained urine causes marked atrophy, first of medulla and later of cortex. The nephrons disappear and are replaced by fibrous tissue.

*Hypertrophy* of the kidney is compensatory. It is seen in its most extreme form when one kidney has been removed, is congenitally absent, or shows marked hypoplasia. In congenital absence of the kidney the weight of the surviving kidney may equal that of the two kidneys. There is no increase in the number of glomeruli and tubules, but they become larger. Between areas of arteriosclerotic atrophy the remaining portions may show a good deal of hypertrophy, which is most readily recognized in the convoluted tubules. The lining cells become larger, the lumen is dilated, and papillary growths may project into the lumen.

**CONGENITAL ANOMALIES OF THE KIDNEY**

*Fetal lobulation* is the most common anomaly. The furrows which separate the original lobules fail to disappear, so that the surface remains lobulated. (Fig. 319.) *Horse-shoe kidney* is also common. The kidneys are fused together, usually by their lower poles. The ureters pass down in front of the connecting bridge of tissue. *Agnesia* or absence of one kidney is usually associated with absence of the ureter. The other kidney is double the normal weight (compensatory hypertrophy). *Aplasia* or marked *hypoplasia* is not very rare. The kidney may be a mere structureless rudiment, or may appear to be a normal small kidney. The other kidney is correspondingly large. *Dystopia* means displacement of the kidney, but the displacement is not active; the kidney has failed to migrate upward to its normal position, and remains in its primitive position, usually at the pelvic brim or the bifurcation of the aorta. The ureter is naturally short, for it has never been of normal length, and as vascularization of the kidney does not occur until the final resting place is reached, the vessels will usually come off the lower end of the aorta. *Congenital cystic disease*, the most important of all the congenital anomalies of the kidney, has already been described.



FIG. 319.—Fetal lobulation of the kidney.

## RENAL PELVIS, URETER, AND BLADDER

The pelvis of the kidney, the ureter, and the bladder are so closely related embryologically, functionally, and structurally that it is natural that the pathological conditions from which they suffer should be very similar. All are lined by stratified squamous epithelium, for the function of all three is either conduction or storage of urine, not secretion or absorption.

**Effect of Obstruction.**—Obstruction to the outflow of urine may cause dilatation of the bladder, ureter, or pelvis of the kidney (hydronephrosis), depending on the site of the obstruction. The obstruction may be in the urethra, bladder, or ureter. In the male urethra obstruction is due to *urethral stricture*, nearly always gonorrheal in origin. In the bladder the common cause is *enlargement of the prostate*, but a *tumor of the bladder* may obstruct the opening of one, sometimes both ureters, producing hydronephrosis. A *calculus* may block the renal pelvis, ureter, or urethral opening in the bladder. *Stricture of the ureter* may be due to scarring following injury caused by the passage of a calculus, or, as shown by Hunner, there may be local inflammation of the wall of the ureter due to hematogenous infection with the formation of one or more strictures (Hunner stricture of ureter). Stenosis of the lower end of the ureter for no apparent reason is probably congenital. *Movable kidney*, a condition in which the normal supports of the kidney are relaxed, allowing the organ to slip downward, may lead to kinking of the ureter and intermittent hydronephrosis. An *aberrant renal artery* passing across the ureter to the lower pole of the kidney may in exceptional cases cause sufficient pressure on the ureter to produce hydronephrosis. It is evident that if the obstruction is in the urethra or bladder the hydronephrosis will be bilateral, whereas if it is in the ureter or the ureteric opening in the bladder, the hydronephrosis will be unilateral.

Obstruction in the urethra (male) leads to dilatation and hypertrophy of the bladder. The proportion varies, just as it does in the gall-bladder and other hollow viscera when they are obstructed. The natural tendency is to dilatation, but there is a compensatory muscular hypertrophy, although this may be largely absent in old men. The hypertrophy leads to marked thickening of the wall of the bladder, and bands of muscle which normally have a reticulated arrangement under the mucosa become very prominent and stand out as trabeculae. The trabeculae are separated by depressions, and one or more of these may become enlarged so as to form a diverticulum. The dilatation of the urinary tract extends to the ureters and to the pelvis of the kidney. Infection is a common complication owing to the accumulation of stagnant urine, and the bladder, wall of the ureter and pelvis of the kidney show an inflammatory thickening in addition to the dilatation. The real danger of obstruction is its effect on the kidney, and this will now be considered.

**Hydronephrosis.**—This is a dilatation of the renal pelvis and calyces with destruction of the kidney substance. (Fig. 320.) Hydronephrosis is caused by obstruction to the outflow of urine. It used to be thought that this obstruction could be either organic or functional, but the idea of a functional obstruction at the pelvi-ureteric junction due to over-action of the sympathetic system has now been abandoned.



FIG. 320. — Hydronephrosis. The renal pelvis and calyces are dilated. The ureter is blocked by a calculus.



FIG. 321.—Hydronephrosis, showing disappearance of tubules.  $\times 65$ .

The obstruction may be congenital or acquired. *Congenital* obstruction takes the form of valve-like folds of the mucosa which are present in the fetus and sometimes at birth, or definite constrictions. These lesions, which are readily overlooked by the pathologist unless searched for with particular care are commonest at the pelvi-ureteric junction, but also occur at the pelvic brim and in the intravesical portion of the ureter. The most extreme examples of hydronephrosis belong to this group, because the condition is symptomless until it becomes far advanced.

*Acquired* obstruction may take the form of: (1) obstruction in the *urethra* from stricture and enlargement of the prostate; (2) obstruction in the *bladder* due to a calculus or to the internal sphincter being unable to open owing to neuromuscular dysfunction (tabes, injury to cord, etc.); (3) obstruction in the *ureter* due to a stone at the upper or lower end, stricture of the ureter, pressure of an aberrant branch of the renal artery, or kinking of the ureter. The most extreme forms

of dilatation are caused by gradual partial obstruction, but sudden complete obstruction, as from ligation of the ureter, may lead to a moderate degree of dilatation followed by hydronephrotic atrophy. If renal ischemia is added to urinary obstruction, the destruction of tissue is much more rapid. Experimental ligation of the posterior branch of the renal artery causes infarction of from one-third to one-half of the kidney; when this is combined with total ureteral obstruction enormous sacculations of the infarcted area are produced in a remarkably short time (Hinman and Hepler).

The pelvis and calyces are dilated, sometimes to an enormous extent. The normal pelvis has an average capacity of 7 to 10 cc., but it may be distended so as to contain several liters. The pyramids are first destroyed by the dilatation of the calyces, and the cortex follows, until finally the kidney is converted into a thin-walled lobulated bag of watery fluid, the greatly distended calyces being separated by incomplete septa. Ischemia produced by pressure of the retained fluid is probably a large factor in the atrophy and destruction of the renal parenchyma. If infection is superadded the condition becomes an infected hydronephrosis. The wall of the sac will be thicker and the lining more rough as the result of infection.

*Microscopically* the first change is marked atrophy of the tubules, while the glomeruli may appear fairly normal. This dissociation of lesions may be very striking, and is peculiar to hydronephrosis. (Fig. 321.) In course of time the glomeruli become fibrosed, and the renal parenchyma is replaced by fibrous tissue. Even in the advanced stages small areas can be found in which the glomeruli and tubules are apparently normal, and are probably continuing to secrete urine.

One of the problems of hydronephrosis is how it is that the contents of the hydronephrotic sac are fresh and clear instead of stagnant and stinking. Moreover, normal secreting tissue can be found even in cases of complete obstruction. It is evident that *absorption* of the fluid must occur, thus allowing of a continual circulation. It has always been thought that this absorption must take place through the tubules, but Hinman and Lee-Brown have shown that absorption in hydronephrosis takes place from the pelvis directly into the veins. This *pyelovenous backflow*, as Hinman calls it, occurs from the minor calyces into the straight veins at the base of the pyramids. By using this mechanism the entire venous system of the kidney can be injected through the hydronephrotic pelvis.

**Inflammation.**—Infection of the pelvi-vesical tract may occur from the urethra, kidney, or neighboring organs. The short female urethra accounts for the frequency of lower urinary tract infection in women and children. In the male, infection from below is due to retention (stricture of urethra, enlarged prostate), or the passage of an infected catheter. Infection of the bladder usually comes from the kidney, unless there is some predisposing cause in the bladder such as retention or stone. The healthy bladder is remarkably resistant to infection, and when pyogenic bacteria are introduced into its cavity they rapidly

disappear. Occasionally infection may come from a neighboring organ, as in inflammation of the appendix or the female pelvic organs. The common infecting organism is *Bacillus coli*, with an acid urine. The pyogenic cocci are next in frequency, and they turn the urine alkaline owing to the production of ammonia. Two of the most troublesome organisms are *Bacillus proteus* and *Bacillus pyocyaneus*, because, being Gram-negative, they are resistant to penicillin. Fortunately they have been found to respond to treatment by streptomycin.

Inflammation of the bladder is called *cystitis*, while inflammation of the renal pelvis is *pyelitis*. The inflammation may commence in the pelvis and infect the bladder, or begin in the bladder and pass to the kidney. We have already seen that in primary renal infection the pyelitis is part of a pyelonephritis. Similarly when the infection ascends from the bladder to the pelvis, the medullary portion of the kidney is involved, so that a pyelonephritis develops.

*Cystitis* may be acute or chronic. In the *acute form*, which is likely to be due to the pyogenic cocci, the mucous membrane is swollen, red, and hemorrhagic. Small ulcers develop, the surface is covered with shreds of epithelium, and small clear cysts are formed on the trigone. Microscopically there is congestion of the submucosa and infiltration with inflammatory cells, the superficial layers of mucosa may be desquamated, but the main substance of the wall is intact. In *chronic cystitis* the appearance depends on the presence or absence of obstruction. When there is no obstruction the wall is thickened owing to the formation of inflammatory tissue; the size of the cavity becomes smaller instead of larger. When there is obstruction as well as inflammation, the bladder is dilated and the wall may be either thickened or atrophied. Polypoid masses of hypertrophied mucous membrane may project into the cavity. The trabeculation, pouching, and formation of diverticula have already been described. Microscopically the mucosa shows patchy ulceration, with areas of granulation tissue formation corresponding to the polypoid masses, the submucosa is fibrosed and infiltrated with chronic inflammatory cells, and the fibers of the muscular coat are separated by an abundant formation of connective tissue.

**Pyelitis Cystica.**—Occasionally numerous tiny cysts may be observed in the renal pelvis, a condition known as pyelitis cystica. Similar lesions occur in the ureter (ureteritis cystica) and bladder (cystitis cystica). As the result of chronic inflammation the epithelium grows down to form small nests of cells. These cells are then arranged to form glands, which develop into cysts.

**Hunner's Ulcer.**—This condition is also known as *interstitial cystitis*, "elusive" ulcer owing to the fact that both symptoms and ulcer may come and go, and by still other names. The cause and nature of the disease are unknown. The affected area shows marked inflammatory thickening, and in the center there is a minute exquisitely tender ulcer, often little more than an erosion. The microscopic changes are those of chronic inflammation. The most important sign of this crippling and chronic condition is bleeding from the lesion seen with the cystoscope when the bladder is distended. The urine contains neither pus nor bacteria.

**Leukoplakia** is a rather rare accompaniment of chronic inflammation. It may be confined to the renal pelvis or bladder, or it may involve pelvis, ureter and bladder. The mucosa is pale and wrinkled so as to resemble skin, and the change is usually patchy with rather clean-cut areas. It is an epidermoid change, a metaplasia of the transitional type of epithelium to a squamous stratified type. Both in the renal pelvis and in the calyces it may be a precursor of the non-papillary type of carcinoma, so that it may be regarded as a precancerous condition.

**Tuberculosis.**—Tuberculosis of the *renal pelvis* occurs at an early stage of tuberculosis of the kidney, for the initial lesion in the pyramid soon spreads to one of the calyces. In the *ureter* the infection spreads in the submucosa, with ulceration of the overlying mucous membrane and eventual cicatrization. The entire wall is rigid and fibrosed, and the ureter may remain wider than normal instead of being stenosed. The chief lesions are usually in the upper or the lower third.

In the *bladder* the infection is usually secondary to renal tuberculosis, but it may come from the prostate, seminal vesicles, and epididymis, and in rare cases from adjacent pelvic organs, *e. g.*, Fallopian tubes. In renal cases the disease begins at the ureteric opening, in prostatic cases it begins at the neck of the bladder. In the common renal cases an area of hyperemia and swelling is first seen around the opening of the ureter, followed by the appearance of tubercles and vesicles. The opening of the ureter may project like a crater into the bladder. The tubercles are formed in the subepithelial tissue, and the overlying epithelium becomes ulcerated. The tuberculous ulcer has a round outline, ragged, overhanging edges, and a gray, shaggy floor. Most of the symptoms of renal tuberculosis are due to bladder irritability. If the kidney is removed and the continued reinfection of the bladder stopped, the vesical lesions may heal completely if the disease has not gone too far. The urine is acid, but septic infection may be superadded, when the reaction will become alkaline.

**Parasites.**—Infection with *Bilharzia hæmatobia* (*Schistosoma hæmatobium*) is very common in some tropical countries, particularly in Egypt. The characters of the parasite are described in Chapter VIII. The ova pass in large numbers from the vesical veins, where they are laid by the female, into the subepithelial connective tissue of the bladder. Here their sharp spines excite great irritation, as a result of which granulation tissue is formed which causes great thickening of the mucosa, as well as papillary vascular projections, from which bleeding readily occurs when the bladder contracts. Hematuria is therefore a constant symptom, and the ova are readily recognized in the urine. Carcinoma is a fairly common development, and offers a good example of the relation of cancer to chronic irritation. Bilharzial lesions may occur in the ureter and renal pelvis. *Eustrongylus gigas*, a round worm, is a fairly common parasite in the renal pelvis of animals, and in rare cases has been found in man.

**Calculus.**—A urinary calculus may be formed in the renal pelvis or the bladder. It may cause symptoms in the kidney, ureter, or bladder. It consists of a nucleus of organic material around which urinary salts are deposited in concentric layers, which are bound together by a colloid matrix of organic matter. The salts, although crystalline in the urine, are in the form of amorphous granules in the



calculus. Urinary calculi may consist of: (1) uric acid and urates, (2) calcium oxalate, and (3) calcium and ammonio-magnesium phosphate. These constituents are often combined. The center of the stone may consist of uric acid or oxalate, with on the outside phosphates the result of infection and decomposition of the urine.

The *uric acid stone* is of moderate hardness, brown in color, and shows concentric rings on the cut surface. The uric acid is usually combined with urates and sometimes with oxalates. It occurs in acid urine. The *oxalate stone* is the commonest form of calculus and consists of calcium oxalate. It is extremely hard, and the surface is rough or may be spiny (mulberry calculus). On this account it produces marked irritation, and is often dark because of staining with blood. The cut surface shows concentric laminæ, but not so clearly defined as in the uric acid variety. The outer layers often contain urates. The *phosphatic stone* consists of calcium phosphate and triple phosphates (ammonio-magnesium phosphate). It is quite different from the others, for it is white, smooth, chalky, and easily broken up. It occurs in alkaline urine. Deposits of phosphates are often formed on the surface of uric acid and oxalate stones owing to a change in the reaction of the urine, the result of infection. The uric acid and oxalate stones occur apart from gross infection in the renal pelvis and sometimes in the bladder, and are known as *primary stones*. The phosphatic stone is formed as the result of infection usually in the bladder but sometimes in the renal pelvis, and is therefore called a *secondary stone*.

*Etiology.*—The etiology of urinary calculi is by no means clear, but four possible factors may be considered: (1) infection, (2) high concentration of urinary salts, (3) vitamin A deficiency, (4) parathyroid tumor. *Infection* is all-important in the secondary phosphatic stone which is a common consequence of the cystitis associated with enlargement of the prostate. Rosenow and his associates have produced renal calculi by isolating streptococci from the urine of calculous patients and implanting them in the devitalized teeth of dogs. It is probable that a mild infection is the starting-point of most if not all the uric acid and oxalate stones in the kidney, although it is not readily detected like the gross infection which is responsible for the secondary phosphatic stone. Ordinary pyelitis (pyelonephritis) is seldom associated with stone formation. It is much commoner in women, whereas renal calculus is commoner in men. The type of stone depends much on the reaction of the urine, and that depends on infection. A uric acid or oxalate stone is formed when the urine is acid. Infection with pyogenic cocci turns the urine alkaline, and the stone becomes coated with phosphates. Subsequent infection with the colon bacillus may bring back an acid reaction, with the deposition of uric acid or calcium oxalate. In this way a stone may contain all three principal constituents.

The *concentration of crystalline salts* is a second factor, although the urine may be loaded with various crystals for long periods without

the formation of a stone. The experimental administration or injection of oxalates has been followed by the formation of small oxalic stones in rabbits. The relation of the colloids of the urine to the crystalloids is probably of great importance, and this in turn is dependent on infection. The presence of an abnormal colloid or the absence of a normal one may cause the crystalloids to be precipitated, especially if they are present in excess. *Parathyroid tumor* is a possibility which must be considered in every case of renal calculus, especially if bilateral and recurring. As a result of the hyperparathyroidism calcium is removed from the bones, the blood is flooded with calcium, and this tends to be deposited in the renal pelvis. Such stones will contain a high proportion of calcium and phosphorus. A serum calcium above 11.5 and phosphorus below 3.5 in a case of renal calculus should suggest the possibility of parathyroid tumor. About 10 per cent of renal calculi are said to be due to hyperparathyroidism. *Vitamin A deficiency* is a cause of renal calculi in the experimental animal. Lack of this vitamin leads to keratinization and desquamation of the epithelium of the renal pelvis which may form the nidus for a stone. It also affects the urinary colloids, so that they fail to hold the crystalloids in solution. It is probable that vitamin deficiency is responsible for some of the peculiarities in the geographical distribution of urinary calculus.

Randall points out that a small "milk patch," usually not more than 2 mm. in diameter, may sometimes be seen on a papilla. This corresponds with a deposit of calcium in the cells lining the tubules. The epithelial covering becomes lost, and a tiny black dot is seen on the milk patch. On this basis a secondary crystalline deposit, the true stone, is formed, which tends to undermine the patch so that the latter is finally torn away. It seems probable that at least some renal stones may originate as a so-called Randall plaque. Anderson has shown that microscopic calculi can be demonstrated in the papillae of every kidney which is examined sufficiently carefully. The fact that large or symptomatic kidney stones are so uncommon indicates that some still unknown metabolic or other systemic factor is necessary for the deposition of large quantities of urinary salts on the nidus.

The *geographical distribution* of stone is striking, and probably related in part to vitamin deficiency. In Egypt and in some parts of India it is common, but in North America it is comparatively rare. In eastern countries urinary stones are commonest in children, while in Europe and North America they occur in the later years of life and are seldom seen in children. A hundred years ago stone formation was common among European children. The change is probably due to the great improvement in the diet of the modern child.

**Stone in the Kidney.**—A renal calculus is formed in the pelvis. It is usually uric acid or oxalate in type, and is much commoner in men than in women. It may be single or multiple, and may remain in the kidney or pass down into the bladder. During its passage along the ureter it excites violent spasmodic contractions which are respon-

sible for the pain of renal colic. The large stone is unable to enter the ureter and is therefore often a silent stone. "It is the little stones, like little dogs, that are likely to make the most noise." (Cabot.)

The chief *effects* on the kidney are retention, infection, and ulceration. If the stone blocks the opening of the ureter *hydronephrosis* will result. The stone may increase in size, and sometimes has a branched appearance owing to extensions into the dilated calyces; this type is known as a coralline calculus. (Fig. 322.) If the stone is impacted in the ureter so as to cause complete obstruction, there may be anuria and atrophy of the kidney. Infection is a common accompaniment of calculus, and by altering the reaction of the urine it may alter the external composition of the stone. If dilatation of the pelvis has not occurred, the infection will cause *pyelonephritis*. If dilatation has occurred there will be *pyonephrosis*. Pressure of the stone on the kidney causes *ulceration*. Much of the kidney may be destroyed in this way even without much infection. The stone has been known to ulcerate through the wall of the pelvis and pass into the abdominal cavity.

**Stone in the Ureter.**—The calculus may be arrested in the ureter as it passes downward. This usually occurs at the upper end or at the lower end where the ureter is constricted in its oblique passage through the bladder wall. The

pressure of the stone causes ulceration of the wall. The ureter above the obstruction becomes dilated, and impaction of a ureteral calculus is the cause of some of the most extreme forms of hydronephrosis.

**Stone in the Bladder.**—A vesical calculus may form in the bladder, or it may originate in the renal pelvis, pass down into the bladder, and there grow greatly in size. There may be one or many stones. The stone which begins in the bladder usually consists of phosphates, and forms in the alkaline infected urine which is retained in enlargement of the prostate and stricture of the urethra. A stone which has reached the bladder from the kidney is usually a uric acid stone, but may be an oxalate stone. In the bladder it gives rise to infection, so that phosphates are deposited on the surface, and the cut surface shows a white outer zone of phosphate and a laminated dark nucleus of uric acid or oxalate. A vesical calculus may reach a very great size. The *effect of the bladder* is the same as in the renal pelvis, *i. e.*, there may be retention due to obstruction of the urethral opening, infection, and ulceration from pressure. The most characteristic symptom is hemat-



FIG. 322.—Large coralline calculus in renal pelvis extending into the calyces.

uria, owing to irritation of the mucosa each time the bladder contracts. On the other hand, it is remarkable how silent a large smooth phosphatic stone may be. The irritation of the stone does not predispose to tumor formation.

**Tumors.**—Tumors of the renal pelvis, ureter and bladder are of the same type, for all are lined by the same transitional epithelium. The bladder tumors are much the most common, and they will be described as the type. They may be divided into three groups: (1) papilloma, (2) papillary carcinoma, (3) non-papillary carcinoma. In a study of 280 cases Aschner found 90 papillomas, 137 papillary carcinomas, and 43 non-papillary carcinomas. It is often very difficult to decide if a biopsy specimen should be placed in the first or second group, and the coagulation produced by the transurethral punch used to remove the tissue makes the differentiation still more difficult. A benign papilloma has a strong tendency to become carcinomatous. For these reasons it is best to regard all epithelial tumors of the bladder as potentially malignant.

Chronic irritation appears to be a distinct etiological factor in many cases. The irritant may be chronic cystitis, sometimes associated with leukoplakia, the ova of *Bilharzia hæmatobia*, or aniline dye excreted in the urine. Workers in aniline dye factories are prone to develop the disease, the lung being the chief route of absorption. The carcinogenic substance in the dye is now known to be beta-naphthylamine. Dogs fed or injected with beta-naphthylamine develop tumors of the bladder but not of the kidney (Heuper, *et al.*). It is of interest to note that the injection of beta-anthraquinoline produces kidney tumors but not bladder tumors (Sempronj and Morelli). There is no relation between carcinoma of the bladder and vesical calculus.

The *villous papilloma*, which by some is regarded as a Grade 1 carcinoma, is a delicate many-fingered growth which springs from a small area of mucosa and unfolds its fragile processes when the bladder is filled with water, until it looks like a piece of seaweed floating in a marine pool when viewed with the cystoscope. In other cases the pedicle is broad and the processes more squat, so that the tumor has a raspberry appearance, whether from diffusion of the irritant or from the implantation of the growths it is hard to say. There is said to be a strong tendency to implantation of tumor cells, as the surgeon may discover after he has "successfully" removed the tumor, but it is more probable that the growth of subsequent tumors is evidence of multicentric origin rather than that implantation of tumor fragments have occurred on so smooth a surface. The usual sites are: (1) just external to the openings of the ureters, (2) at the neck of the bladder, and (3) in the vault. The villi consist of a very delicate framework of connective tissue containing large capillary loops and covered by transitional epithelium. (Fig. 323.) It is easy to understand how easily these fragile processes are injured when the bladder contracts, so that hemorrhage from the capillary loops is the essential symptom.

The *papillary carcinoma* is the commonest form. It usually arises

from a benign papilloma, the change occurring in any part of the tumor. The tumor may be infiltrating or non-infiltrating. It is the latter which may resemble so closely the benign papilloma. Indications of malignancy are a departure from the normal histology (loss of palisade arrangement), variations in the size, shape, and staining characters of the cells, hyperchromatic nuclei, and the presence of numerous mitotic figures.

The *non-papillary carcinoma* is the least common form. The tumor extends under the mucosa and infiltrates the wall deeply. There is necrosis and ulceration, so that the tumor may take the form of a carcinomatous ulcer. Microscopically it may be scirrhus or medullary in type. An epidermoid carcinoma may develop on top of a leukoplakia. The rarest epithelial tumor is an *adenocarcinoma* developing from glands occasionally present in the trigone of the bladder.

Involvement of the opening of the ureter on each side leads to urinary retention and hydronephrosis, and as infection is easily added there is likely to be cystitis and pyonephrosis. Death may be due to uremia.

**Spread.**—Spread occurs to the iliac and lumbar glands. The lungs and liver may be infected through the blood late in the disease. There may be secondary growths in the bones. The low-grade form (papilloma) remains confined to the bladder.

*Tumors of the renal pelvis* are of the same type as those which occur in the bladder. So are the rare *tumors of the ureter*. The tumor is usually a malignant papilloma, and the wall of the pelvis may be covered with finely branched villous processes. These are friable and vascular, so that hemorrhage readily occurs. The tumor may block the ureter and cause hydronephrosis. There may be multiple tumors of the renal pelvis and bladder (? implantation). A patch of leukoplakia, sometimes due to the irritation of a calculus, may be the starting point of an epidermoid carcinoma.

*Sarcoma* of the bladder is very rare. It is never papillomatous. *Myxoma* and *leiomyoma* are very rare; the myxoma occurs especially in children. A *dermoid cyst* may occur in the wall, giving rise to the passage of hair in the urine (pilimiction).

**Malakoplakia.**—This very rare condition is characterized by yellow, soft (*malakos*, soft), discrete nodules in the bladder mucosa. In addition to ordinary inflammatory changes the lesions present highly characteristic multinucleated



FIG. 323.—Papilloma of bladder. The thin-walled vessel can be seen in the middle of the villus.  $\times 100$ .

giant cells containing calcified cytoplasmic inclusions known as Michaelis-Gutmann bodies. The condition is associated with cystitis.

**Diverticulum.**—A diverticulum of the bladder is an uncommon condition. In chronic cystitis a certain amount of pouching may occur between the trabeculae of the wall. In the more marked cases it is probable that there is a congenital basis. The diverticulum may be very large, sometimes as large as the bladder itself. The wall may consist of muscle or only of mucous membrane. Carcinoma may develop inside the diverticulum.

**Bone Formation.**—The epithelium of the urinary tract (renal pelvis, ureter and bladder) has a curious osteogenic power. Experimental injury to the renal pelvis is followed by bone formation in the fibrous tissue external to the mucosa. Experimental implantation of bladder mucosa into the abdominal wall leads to bone formation (Huggins). The same result has been observed in rare cases in man after operations on the bladder, *e. g.*, prostatectomy.

## THE URETHRA

### GONORRHEAL URETHRITIS

This is a very acute suppurative condition. By the end of the second day the crypts in the wall of the anterior urethra are filled with pus cells containing gonococci, and by the third day the mucosa is extensively infiltrated, for the columnar epithelium offers no resistance. An acute inflammatory exudate is formed in the mucosa, and an abundance of pus is poured from the surface. The infection spreads in the submucosa until the posterior urethra (membranous and prostatic parts) is involved. Here the infection may linger for a long time in the glands which open on to the surface. The acute inflammation may subside in the course of a few weeks, the desquamated epithelium being replaced by epithelium of squamous type. In other cases the infection becomes chronic, being fed from foci in the posterior urethra. The mucous and submucous coats are converted into granulation tissue, which later becomes fibrosed and scarred. The scar tissue may contract, producing a stricture of the urethra.

*Stricture* usually develops in the bulbous urethra. The narrowing may be extreme, producing the results of obstruction which have already been considered (hydronephrosis, etc.). As there is no residual urine there is less chance of infection than in enlargement of the prostate, but if a catheter has to be used frequently the danger becomes great. When infection does occur, the patient may die of sepsis or of uremia.

Stricture may be due to trauma, or may be congenital (see below).

*Calculus* of the urethra is rare. It is the result of a stone from the kidney or bladder being stopped in the urethra.

### CONGENITAL ANOMALIES OF THE LOWER URINARY TRACT

*Double ureter* is a condition in which the entire ureter or only the upper part is duplicated. There is a double pelvis, one in the upper part of the kidney, the other in the lower. If the doubling affects the entire ureter, there are two separate openings into the bladder. *Congenital dilatation of the ureters* may

be due to a variety of causes. Bilateral dilatation in male children is likely to be caused by a congenital valvular obstruction in the posterior urethra from a persistent urogenital membrane or an exaggeration of the normal mucosal folds of the urethra. Unilateral dilatation may be due to congenital stricture of the ureter at its point of entrance into the bladder wall. The rare condition of *ureterocele* or cystic dilatation of that part of the ureter which lies within the bladder wall is due to congenital narrowing at the mucosal orifice; this gives rise to a characteristic bulging of the bladder wall at that point, which can be readily recognized with the cystoscope. Occasionally no obstruction of any kind can be found to account for the dilatation of the ureter; such cases are attributed to a hypothetical weakness of the neuro muscular mechanism of the wall of the ureter. *Ectopia vesicæ* or *extroversion* of the bladder is a rare condition in which, owing to a congenital deficiency of the anterior wall of the bladder with an associated splitting of the anterior abdominal wall in the middle line, the interior of the bladder is exposed and the posterior wall may be extruded. The epithelium of the exposed mucosa undergoes metaplasia into an epidermoid type. The condition is often associated in the male with *epispadias*, the urethra remaining open on its dorsal aspect; in the female the clitoris may be split. *Patent urachus* is a rare condition in which urine may pass from the bladder to the umbilicus along the original line of the allantois. Only part may remain patent, *e. g.*, the outer or inner ends or the central portion. In the latter variety a cyst of the urachus may result.

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## CHAPTER XXV

### THE MALE REPRODUCTIVE SYSTEM

#### THE TESTICLE AND EPIDIDYMIS

##### INFLAMMATION OF THE TESTICLE AND EPIDIDYMIS

THE testicle and epididymis form one organ although they are developed separately. Inflammation may be practically confined to the epididymis as in gonorrhea, or to the testicle as in the orchitis of mumps.

**Gonorrheal Epididymitis.**—Gonorrhea commences as an acute urethritis, with marked inflammatory change in the subepithelial connective tissue. The infection ascends the urethra and settles in the posterior urethra. The disease may clear up after an acute course of a few weeks, or the infection may linger in the posterior urethra and affect other parts of the genital tract. The epididymis is the chief sufferer, infection occurring usually in the second and third months. The first lesion is at the lower pole, the globus minor, but soon the whole organ is involved. It is seldom that the infection spreads to the testicle, although inflammation of the surrounding fibrous tissue may make that organ feel enlarged and hard. The epididymis is swollen and tender. Hydrocele is often present, and there may be some thickening of the spermatic cord. The type of inflammation is unusual. As the gonococcus is a pyogenic organism, there is suppuration with the formation of minute abscesses, yet there is no extensive abscess formation as might be expected, but rather a widespread inflammatory edema. The inflammation is acute and subsides quickly, but often leaves fibrous scars which obliterate the seminiferous tubules. Fortunately the epididymitis is usually unilateral. When it is bilateral, complete sterility may result.

Other gonorrheal lesions are prostatitis, stricture of the urethra, and blood infection of distant organs. The first two are considered below. Blood infection may give rise to inflammation of joints (gonorrheal arthritis) and of tendon sheaths (tenosynovitis).

**Non-gonorrheal Epididymitis.**—Non-gonorrheal epididymitis is very much less common. It is usually caused by staphylococci, sometimes by streptococci or *Bacillus coli*. The infection is secondary to stricture of the urethra, enlarged prostate, or inflammation of the seminal vesicles. There is abscess formation in the epididymis, marked hardness and thickening of the vas and seminal vesicle, and a tendency to chronicity and recurrences.

**Orchitis.**—Inflammation of the testicle may be due to trauma or to acute infections. *Traumatic orchitis* is caused by a blow, which is

followed by acute inflammatory edema of the organ. The condition is short and acute, but sometimes results in atrophy of the testicle. *Metastatic orchitis* is the term applied to infection from the blood stream which occurs in certain acute fevers. It is usually due to mumps, occasionally to typhoid fever and smallpox, and rarely to other febrile and septic conditions. Sometimes the *orchitis of mumps* has preceded the parotitis. It is usually unilateral, and is rarely seen before the age of puberty, being commonest in young men. The enlargement is not great owing to the firm fibrous tunica albuginea, but the tension is great and the pain correspondingly severe. The epididymis is rarely involved. The lesion is never suppurative, but may be followed by fibrosis and atrophy of the testicle. Infection of *extension* from the posterior urethra may occur. In severe gonorrheal epididymitis there may be slight involvement of the testicle. There may be colon bacillus infection from a cystitis. In these cases the lesions are suppurative.

### TUBERCULOSIS OF THE GENITAL TRACT

As the entire genital tract, sometimes indeed the urogenital tract, may be involved by tuberculosis, it is convenient to consider all the organs together. The infection is usually blood-borne, and starts in the lower pole of the epididymis (Fig. 324), but occasionally in the seminal vesicle. In a small proportion of cases the bacilli spread along the vas from the bladder, which itself is infected from a focus in the kidney. Nodules are formed throughout the epididymis, so that the organ is enlarged and hard. Caseation and liquefaction occur sooner or later, the skin of the scrotum is involved, and a tuberculous fistula is formed. By the time the patient is seen clinically the disease has usually spread throughout the genital tract, so that the vas, seminal vesicles, and prostate are all involved. The *testicle* is not involved early, but in time the disease spreads to it from the epididymis, invading first the body of Highmore. The *spermatic cord* is thickened and nodular. The *seminal vesicle* is involved early, and indeed the infection may commence there. The entire vesicle is usually destroyed. The *prostate* may be infected either from the genital tract or from the kidney. Caseous nodules are formed in the gland with destruction finally. The *tunica vaginalis* may be studded with tubercles, so that a hydrocele is a common accompaniment. The *other epididymis* is often involved at a later stage, probably by way of the lymphatics. The *bladder* shows tuberculous ulcers, especially in the trigone. The



FIG. 324. — Tuberculosis of the epididymis. There is a caseous area in the lower pole and the spermatic cord is thickened.

*kidneys* are occasionally involved by upward spread from the genital tract, but combined genito-urinary tuberculosis usually originates in the kidney, with secondary infection of the genital tract.

### SYPHILIS OF THE TESTICLE

Syphilis of the testicle is common. Unlike tuberculosis it affects the body, seldom the epididymis. It occurs in two forms which may be combined: (1) a diffuse interstitial inflammation, and (2) a gumma. (1) The *diffuse form* is much the commoner, and is indeed one of the common manifestations of syphilis, although usually overlooked because it gives rise to no symptoms. The testicle is not enlarged or tender, but it has a characteristic wooden hardness owing to diffuse fibrosis, and there is a loss of the normal testicular sensation when the organ is squeezed. The tunica albuginea is thickened, and the gland is pervaded with white bands of fibrous tissue, so that the cut surface remains flat instead of bulging forward in the normal manner. Microscopically there is at first a diffuse formation of cellular inflammatory tissue containing many spirochetes, followed later by fibrosis with atrophy and disappearance of the tubules. (2) A *gumma* causes enlargement of the testicle. It is at first gray, but later becomes white and fibrous. Softening is uncommon, and the lesion tends to become scarred.

### TUMORS OF THE TESTICLE

Great differences of opinion exist regarding tumors of the testicle. These cannot be discussed here, and the tumors will simply be divided into two groups without an attempt at justification. For a discussion of the various views the reader is referred to Ewing's book. The two groups into which practically all the testicular tumors fall are the seminomas and the teratomas, of which the former are the commoner. Many workers believe that the seminoma arises from the germinal cells of the seminiferous tubules (hence the name). It seems rather better to regard all testicular tumors fundamentally as teratomas, which may be divided into the simple and the complex. The simple teratomas are more or less homogeneous tumors, which only possess representatives of one primordial germ layer; they include the seminomas. In support of this idea is the fact that one occasionally sees seminomas with cartilage and other structures. Complex teratomas include embryoma and chorionepithelioma. An argument in favor of the teratomatous nature of testicular tumors is the fact that the great majority occur in early adult life, whilst 90 per cent occur before the age of fifty.

**Seminoma.**—Ewing calls this tumor an embryonal carcinoma. It grows slowly and replaces the testicle. The cut surface is fleshy and homogeneous so as to resemble that of a sarcoma. The *microscopic picture* is variable. The cells may be large and clear like spermatocytes, or may be small and dark like the cells of a lymphosarcoma. The arrangement may be tubular in the most slowly-growing tumors,

but diffuse in the rapidly-growing ones. (Fig. 325.) It is evident that the tumor may closely resemble either a sarcoma or a carcinoma. The seminoma of the testicle is homologous with the dysgerminoma of the ovary; they are of similar appearance, and both originate from the early stages of germ cells.

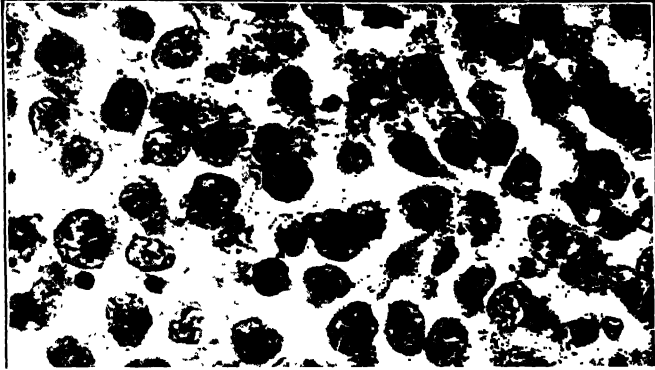


FIG. 325.—Seminoma. The cellular arrangement is anaplastic. The cytoplasm has for the most part disintegrated; only nuclei and nucleoli are seen.  $\times 600$ .



FIG. 326.—Embryoma of testicle. The structure is very varied showing tubular structures, cystic spaces, and cartilage in the center.  $\times 30$ .

**Teratoma.**—This is a teratoid tumor which probably arises from a germinal blastomere or primitive germinal cell. As these cells are totipotent the tumor may contain structures derived from three embryonic layers. It is also called embryoma, mixed tumor of the testicle, and, in the older literature, fibrocystic disease. The tumor may attain a very great size. The cut surface usually presents a characteristic cystic appearance (hence the old name of fibrocystic disease), the cysts varying much in size in different specimens and sometimes being absent. The *microscopic appearance* is extremely varied, though

in some cases the growth is almost confined to one type of tissue. From the *mesoderm* there may be cartilage, bone, plain and striated muscle, fat and lymphoid tissue; from the *entoderm* there may be tubular spaces lined by columnar cells, *i. e.*, abortive attempts at forming an alimentary canal; from the *ectoderm* there may be stratified epithelium with typical cell nests. It is easy to understand how the tumor may be mistaken for a chondroma, myxosarcoma, adenocarcinoma, epidermoid carcinoma, lymphosarcoma, etc. A usual appearance is a mixture of lymphoid tissue, cartilage, and tubular spaces, many of which are dilated to form cysts of varying size. (Fig. 326.) The picture may be that of an *embryonal adenocarcinoma*, in which there is the formation of acini lined by cuboidal or low columnar cells in addition to solid masses of cells.

Both the seminoma and teratoma are malignant tumors, although the latter may show no malignant characteristics for a considerable time. There is lymph spread to the abdominal lymph nodes, and blood spread to the lungs, liver, and other viscera.

An important though puzzling feature of malignant tumors of the testicle is the occurrence of a positive Aschheim-Zondek test in the urine. The reaction is much the most marked in chorionepithelioma (see below), but it may also be present in other testicular tumors. It seems probable that the tumor produces a hormone which stimulates the anterior pituitary to secrete an increased amount of prolan. It is said that the anterior lobe of the pituitary shows hyperplasia of the basophilic cells.

**Chorionepithelioma.**—This rare tumor is a special development of a teratoma in which fetal membranes have been formed, the chorionic epithelium giving rise to the chorionepithelioma. Other structures are also formed, but these tend to be destroyed by the malignant growth. In one case which I studied, typical choroid plexus was present. The tumor usually remains small, and its structure may be obscured by hemorrhage so that it is easily overlooked. The primary tumor may be only a few millimeters in size, but large secondary growths are formed in the lungs, liver, etc. The Aschheim-Zondek test is positive. Gynecomastia (female type of breast development) is common.

**Interstitial-cell Tumor.**—This is a rare tumor which is met with both in man and the lower animals. It tends to be light brown in color. The cells of which it is composed are arranged in solid masses supported by a minimal amount of delicate connective tissue. They are polygonal, intensely acidophilic, and may present a foamy vacuolated appearance owing to the presence of fat. When the tumors develop before puberty there is evidence of sexual precocity, but when they occur at a later period there may be impotence, gynecomastia, and a positive Aschheim-Zondek reaction due to excess of estrogen. They are of slow growth, and are either benign or of a low grade of malignancy. Similar tumors can be induced in mice by the administration of estrogen.

**Testicular Tumors and Sex Hormones.**—Either masculinizing or feminizing effects may be produced by tumors of three organs: the testes, ovaries and adrenals. As a rule such tumors are rich in lipid, and therefore yellow in color. Feminization in men may be caused by a rare tumor homologous with the ovarian arrhenoblastoma (Teilum). An adrenal cortical tumor may produce both estrogenic and androgenic substances. This is not so strange as might appear at first sight, for there is a very close chemical relationship between the steroid compounds which constitute the male and female sex

hormones. A cynic, indeed, has suggested that the only essential difference between Romeo and Juliet was an—OH linkage. Moreover steroids which produce an estrogenic effect are not necessarily identical with estrin.

The presence of the chorionic type of gonadotropin in the urine in a case of testicular tumor indicates that the tumor contains chorionic tissue, for the hormone is only produced by such tissue. (The chorionic type must be distinguished from the castrate type of gonadotropin; the latter, which is produced by the pituitary, occurs in the urine of castrates and of elderly men and women.) Although chorionic gonadotropin may be present in the urine, no chorionic tissue may be found in the tumor. In such a case it is probable that if the entire tumor had been examined microscopically, such tissue would have been discovered. In one such case the metastases alone showed chorionepithelioma (Brewer).

## THE PROSTATE

### INFLAMMATION OF THE PROSTATE

Prostatitis may be acute or chronic. Both forms are usually due to gonococcal infection. The *acute* form is part of an acute posterior urethritis. It is usually mild in type, but some abscesses may be formed, and occasionally there is extensive suppuration. In *chronic* prostatitis foci of chronic inflammatory cells are scattered through the gland, with varying degrees of fibrosis. The prostate is hard, and may be larger or smaller than normal, depending on the amount of scarring which has taken place. In these chronic cases there is often a mixed infection with *Bacillus coli*, staphylococci, etc.

### HYPERTROPHY OF THE PROSTATE

Enlargement of the prostate is very common in men over the age of sixty years, but only in a small number of cases (about 8 per cent) does it cause symptoms. It is essentially a disease of advancing years, and is hardly ever seen in early life. The reason of the hypertrophy is uncertain. It is probably an expression of imbalance of the sex hormones in the male, analogous to cystic hyperplasia of the breast. When estrin is injected into castrated rats there is hyperplasia of epithelium, smooth muscle and connective tissue. These changes do not occur if testicular extract is injected at the same time, nor in normal rats which have not been castrated. This suggests that prostatic hypertrophy in elderly men is due to a disturbance in the balance between the production of testicular hormone and that of estrin (also produced by the testicle). It may be noted that the prostates of children at birth often show similar changes, probably due to estrin from the placenta. The hope is that in the future it may be possible to control prostatic hypertrophy by means of hormone therapy.

The condition of the prostate varies, depending on the proportion of glandular to fibrous tissue, so that it may be large and soft or relatively small and hard. Usually the enlargement is made up of a series of rather spongy nodules with clearly-defined margins; these nod-

ules are clearly seen on the cut surface. Moore emphasizes the marked difference between the lobular architecture, both gross and microscopic, of the normal prostate and the nodular character of benign hyperplasia. The part of the gland containing the nodules enlarges so as to



FIG. 327.—Hypertrophy of the prostate. The gland is considerably enlarged, and the middle lobe projects up into the bladder, the wall of which is hypertrophied.

form a mass which compresses the surrounding tissue, and this in turn constitutes a false capsule which enables the nodular mass to be separated and shelled out with comparative ease. In other cases there is diffuse fibrosis rather than nodular hyperplasia, in which case no nodules can be seen and shelling out is impossible. The lateral lobes may be enlarged or a new *middle lobe* may be formed by hypertrophy of the group of glands which lies in the floor of the urethra. This middle lobe forms a conical mass which projects up from the floor of the bladder, carrying the urethral orifice with it. (Fig. 327.)

The *microscopic appearance* is one of glandular hyperplasia with overgrowth of fibrous tissue and muscle in varying degrees. (Fig. 328.) The picture may closely resemble that of lobular hyperplasia

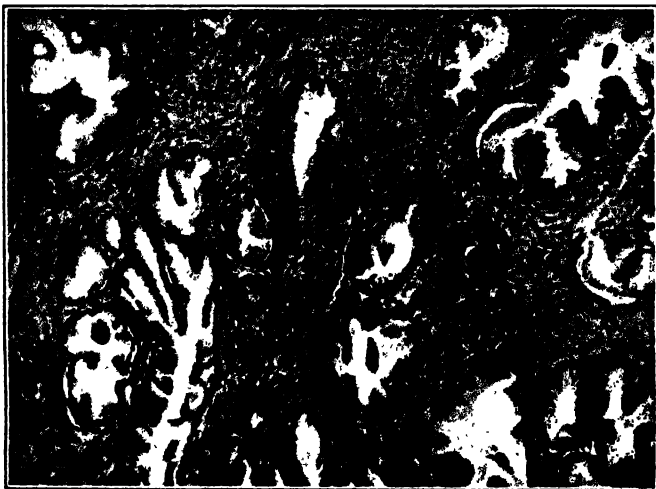


FIG. 328.—Hypertrophy of the prostate. There is marked epithelial proliferation in the acini and ducts.  $\times 60$ .



of the breast. The glandular tissue is increased, the acini are enlarged, and papillary processes of epithelium may project into the lumen. In other cases the glandular tissue is not hyperplastic, but there is a great increase of fibrous tissue and a good deal of plain muscle. Moore, whose studies of the structural variations of the normal prostate are so valuable, considers that the most striking feature of benign hyperplasia is the variation in appearance of the same structure in different parts of the prostate, compared with the uniform appearance of the normal prostate. As infection is a frequent complication, inflammatory foci may be scattered through the stroma.

**Effects.**—Enlargement of the prostate is usually unaccompanied by symptoms. The symptoms when present are due entirely to the position of the gland at the urinary outlet. The effects are felt on the urethra, the bladder, and the kidneys. (1) The *prostatic urethra* may be elongated, compressed to a mere slit, and rendered tortuous. This is the most important cause of obstruction. (2) The *bladder* cannot be completely emptied, because the urinary outlet is lifted up above the surrounding floor and the enlarged middle lobe may exert a ball-valve action. Moreover the vesical sphincter is rendered incompetent through being stretched by the middle lobe which grows up from the floor of the urethra. There is therefore a constant dribbling of urine, and yet the bladder is never empty. The residual urine is readily infected and cystitis results. The bladder becomes hypertrophied in its efforts to overcome the obstruction, and the thick bands of muscle give the wall a ribbed appearance. Later there is dilatation, with pouching of the wall between the bands producing false diverticula. Owing to the cystitis and the stagnation of urine, phosphatic calculi are often formed in the bladder. (3) The *kidneys* suffer because of the obstruction and infection. The ureter and renal pelvis on both sides are dilated, so that hydronephrosis is produced. Infection ascends the dilated ureters, and causes pyelonephritis and pyonephrosis. Renal insufficiency now declares itself, non-protein nitrogen is retained in the blood, and the patient dies of uremia. The back-pressure on the kidney is associated with arterial hypertension, even though the kidney damage is only slight. When drainage of the bladder is established there is a marked fall in the systolic blood-pressure within forty-eight hours.

### CARCINOMA OF THE PROSTATE

Cancer of the prostate is a very common condition. It is often associated with hypertrophy, but the two conditions occur at the same age period, and there is no proof that there is any etiological relationship between them. The prostate may or may not be enlarged when the patient is first seen, but its chief characteristic is its hardness. It cuts with the gritty sensation of a scirrhus cancer of the breast. The cut surface is dry, does not bulge, is not nodular or lobulated, and shows little yellow islands of carcinoma cells like those seen in a scirrhous of the breast. In all these respects it differs

from prostatic hypertrophy. At the same time it must be pointed out that in some cases the gross differentiation is impossible, and that microscopic examination of a number of blocks may be necessary before cancer can be excluded, as the malignant process may be confined to a small part of the gland. Every prostate removed for hypertrophy should be cut up into a series of thin slices and examined for areas of malignancy indicated by increased hardness and lessened elasticity. In routine microscopic examination of the prostate at autopsy Rich found 14 per cent of carcinoma in men of fifty years of age. In many of these the tumor was only a few millimeters in size, so that even if the patient had lived it might not have produced symptoms for a long time. Moore reports 52 cases of occult carcinoma, in only 10 of which could a gross diagnosis be made.



FIG. 329.—Carcinoma of the prostate. This glandular type may be mistaken in its early stages for simple hypertrophy.  $\times 200$ .

The *microscopic appearance* is that of scirrhous carcinoma or adenocarcinoma. The former is much the commoner. The microscopic diagnosis is usually easy, but sometimes it is very difficult to distinguish between benign hypertrophy and commencing malignancy. (Fig. 329.) In the prostate when the pathologist is in doubt about a lesion it is probably malignant; in the breast the reverse is the case. In rare cases the tumor cells are loaded with lipid, giving them a foamy appearance (carcinoma xanthomatodes).

The *spread* is important. The prognosis in cancer of the prostate is very bad. Even when a very early growth is discovered accidentally in a prostate which has been removed for simple hypertrophy,

the patient is likely to die of recurrence or metastases. Radiation gives no better results than surgery. In about 70 per cent of cases there is invasion beyond the capsule when the patient seeks medical advice. Even at the first examination it is common to find invasion of the bladder urethra, seminal vesicles, rectum, rectovesical pouch, omentum, or bony pelvis. The spread is both local and distant. The growth usually starts in the posterior part of the gland and spreads up along the line of the ejaculatory ducts; it appears between the bladder and the seminal vesicles where it can be felt on rectal examination. The floor of the bladder and the surrounding fibrous structures are invaded. An important method of spread is along the perineural

lymphatics, which can often be seen distended with cancer cells. Perineural invasion of the capsule is one of the earliest changes, no matter how small the primary tumor may be. The pelvic and lumbar lymph nodes are involved early, and there may be lymph spread to the thoracic and even the supraclavicular nodes. The inguinal nodes are involved in about 15 per cent of cases, probably due to lymphatic connection with the seminal vesicles and urethra and retrograde transport from these areas. It is evident that hardly a node in the body may escape. Metastases are formed in the liver, lungs, etc., by blood spread. But the commonest distant metastases are in the bones. In about 70 per cent of autopsies the skeleton is found to be involved. The pelvis and lumbar vertebræ are the commonest sites, followed by femur and ribs. Spread to the sacrum and lumbar vertebræ may in some cases be by way of the perineural lymphatics, but, as Batson has pointed out, a more frequent route is probably the vertebral system of veins. When an elderly man is found to be suffering from a tumor of bone, the prostate should always be examined. Moreover the bone metastases in cancer of the prostate are different from those in other secondary carcinomas; the former are sclerosing in type, while the latter are rarefying; a distinction which can be readily recognized radiologically.

**Sex Hormones and Prostatic Carcinoma.**—The development and activity of the prostate is dependent on stimuli from the testes. Castration before puberty prevents development of the prostate, and castration in adult life causes regression of the normal gland and decrease in size in cases of prostatic hypertrophy. Huggins and his associates have applied these facts to the problem of the control of cancer of the prostate with remarkable results. In a series of cases orchidectomy was followed not only by an astonishing improvement in the subjective condition (bone pain, etc.), but also by such objective evidence as a great and permanent fall in the acid phosphatase in the blood and a shrinkage of the primary lesion. Injection of large amounts of estrogen has a similar effect on the acid phosphatase and to a lesser extent on the physical condition, owing apparently to neutralization of androgens which have an opposite effect.

A direct relationship between carcinoma of the prostate and male gonadal activity is revealed by studies on the enzyme *phosphatase*. For long it has been known that phosphatase is found in abundance in growing bone and cartilage. It is also present in the circulating blood, and in certain of the osteodystrophies, particularly Paget's disease, the level in the blood is markedly raised. Two varieties of the enzyme can be distinguished, alkaline phosphatase with an activity maximum at pH 9, and acid phosphatase with an activity maximum at pH 5. The *alkaline phosphatase* is that present in growing bone and is apparently produced by osteoblasts; the only conditions in which it is known to be increased in the blood are certain types of bone disease (especially Paget's disease) and liver disease. The level in the blood may be raised in prostatic cancer owing to bone involvement by metastases. The *acid phosphatase* was originally found in the spleen and kidney of swine and cattle, but far the greatest concentration is in the prostate where it is apparently produced by the prostatic epithelium. A similarly large amount is found in carcinoma of the prostate. The enzyme can be demonstrated microscopically in the epithelium of both the normal and malignant gland by Gomori's method. In cases where the carcinoma is disseminated in the bones, particularly the bony pelvis, there is a marked rise in the acid phosphatase in the serum. Such a rise has been observed in no other condition. Huggins and his associates claim that when acid phosphatase is present in activity greater than 10 units

in 100 cc. disseminated prostatic cancer is present. The increase in the blood is not found in every case.

**Sarcoma.**—Sarcoma of the prostate is very rare. It is probable that most of the tumors which in the past have been called sarcoma are examples of anaplastic, undifferentiated carcinomas.

**Prostatic Calculi.**—Prostatic calculi may form in the ducts of the gland. They are usually minute and give rise to no symptoms.

## PENIS AND SCROTUM

### CARCINOMA OF THE PENIS AND SCROTUM

*Cancer of the penis* begins on the glans or prepuce. The tumor shows a striking geographical distribution, being rare in the Americas and Europe, but common among the Chinese, Malays, African negroes, and in India. It is extremely rare among peoples who practise circumcision; thus it is rare in Mohammedan Hindus (circumcised), common in Buddhist Hindus (non-circumcised). In over 70 per cent of cases phimosis is or has been present, a good example of the relation of chronic irritation to carcinoma. The lesion takes the form of a small wart at first, but a large fungating mass is formed later. The tumor is an epidermoid carcinoma. Secondary growths occur in the inguinal and later in the retroperitoneal lymph nodes. Blood spread is later still. *Cancer of the scrotum* used to occur in chimney sweeps and still does in workers with coal tar and paraffin, owing to the continued irritation.

### HYDROCELE

A hydrocele is a collection of fluid in the tunica vaginalis. It may be acute or chronic in type. The *acute* cases are due to spread of infection usually from the epididymis, occasionally from the body of the testicle, to the tunica vaginalis. The two infections commonly associated with acute hydrocele are gonorrhea and tuberculosis. The fluid, which is moderate in amount and somewhat turbid owing to the presence of pus cells, accumulates rapidly. The *chronic* variety is probably due to some low-grade infection, but this is not susceptible of proof. The fluid is clear and watery, rich in albumin, and may be so abundant as to cause great distention of the scrotum. It may contain shimmering cholesterol crystals, and in some cases fibrinous bodies may separate out. The sac tends to become greatly thickened, especially if there has been repeated tapping. In long-standing cases the pressure on the testicle may lead to atrophy.

*Encysted hydrocele of the spermatic cord* is a collection of fluid in an unobliterated portion of the processus vaginalis between the testicle and the internal abdominal ring. It does not communicate with the tunica vaginalis.

**Hematocoele.**—Hematocoele is the name given to hemorrhage into a hydrocele. The hemorrhage is usually due to trauma of some kind. This may be a direct blow or kick, or it may be the result of tapping the hydrocele. In the latter case there is either injury to a vein by the

needle, or the sudden reduction of pressure outside an unsupported vessel may cause it to give way. Sometimes the hemorrhage may occur spontaneously. The cavity of the tunica vaginalis is occupied by breaking-down blood clot, and the walls are covered by ragged deposits of fibrin.

### SPERMATOCELE

A spermatocele is a cystic dilatation of the spermatic ducts of the epididymis. The cyst is single or multilocular, and is situated at the upper end of the testicle. The fluid, which contains hardly any albumin, is of a peculiar milkiness owing to the presence of great numbers of spermatozoa.

### VARICOCELE

This is a varicosity of the pampiniform plexus of veins in the spermatic cord. There is a primary and a secondary form. The *secondary* form is due to pressure on the spermatic vein, usually by a tumor of the kidney because of its proximity to the termination of that vein. It therefore is commoner over middle age. The *primary* form is very much more frequent. It is called primary because the cause is unknown. It is common in young unmarried men, and may be related to the congestion caused by unrelieved sexual stimulation. It is nearly always on the left side, so that a varicocele on the right side should suggest the presence of a tumor. The left spermatic vein enters the renal vein at right angles; the right spermatic vein enters the vena cava obliquely. There is therefore more resistance to the outflow of blood from the left vein. A loaded rectum may also press on the left vein. The veins of the plexus are elongated, tortuous, and feel like a bag of worms. They empty when the patient lies down. Thrombosis is rare.

### OTHER LESIONS OF THE PENIS AND SCROTUM

**Phimosis.**—Phimosis or narrowing of the prepuce is a congenital condition. In the more severe cases there may be marked urinary obstruction with hypertrophy of the bladder, dilatation of the ureters and hydronephrosis. The relation to carcinoma has already been mentioned.

**Calcareous Deposits.**—Calcareous deposits in the penis may occur in old people. They correspond to formations of bone in the lower animals.

**Syphilis.**—The primary chancre of the penis has already been described in Chapter VII. A primary chancre sometimes occurs in the scrotum, but secondary lesions (condylomata) are much more frequent. The scrotum may be involved in a gumma of the testicle.

**Congenital Anomalies.**—*Undescended testicle* is a condition in which the testicle is arrested at some point in its descent. This may be in the neighborhood of the kidney, at the internal abdominal ring, in the inguinal canal, or at the external abdominal ring. The inguinal canal is much the commonest position. Here the testicle is exposed to trauma and therefore liable to attacks of orchitis. An undescended testicle is unusually prone to develop a malignant tumor. The gland is atrophic and the spermatogenic cells disappear, so that if the condition is bilateral the person is sterile. Virile power is retained, however, for the interstitial cells of Leydig do not share in the atrophy; indeed, they often appear to be more numerous than usual, and the best place to see these cells is in an undescended testicle. (Fig. 330.) Cryptorchism (non-descent of testicle) is now known to be due in some cases to lack of the gonadotropic hormone of the anterior pituitary which regulates the process. Admin-

istration of the hormone may be followed by descent of the testes. Curiously enough the gonadotropic hormone is present in the urine of these boys and disappears under the treatment (Hess). It is known that when the testes have been removed (or are undescended) there is an excessive secretion of gonadotropic hormone. *Epispadias* is incomplete closure of the urethra on the dorsal aspect of the penis. *Hypospadias*, which is more common, is the

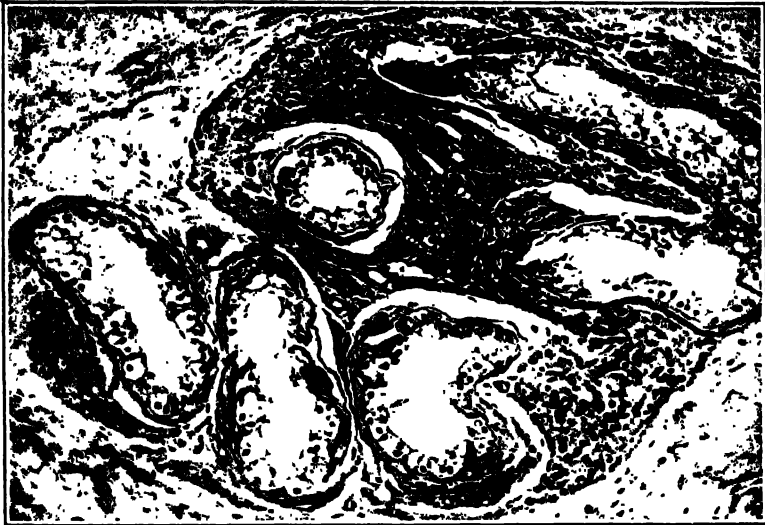


FIG. 330.—Hypertrophy of interstitial cells in undescended testicle.  $\times 100$ .

same condition on the ventral aspect. *Hermaphroditism* is a blending of the male and female sexual organs. In very rare cases testicles and ovaries have been present together. The usual arrangement is for the gonads of one sex to be associated with the secondary sexual characters of the other. The commonest form is that in which the scrotum is split so as to resemble the labia majora, the penis is rudimentary, the testicles are undescended, and the secondary sex characters are of the female type.

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## CHAPTER XXVI

### THE FEMALE REPRODUCTIVE SYSTEM

#### THE UTERUS

**Menstruation.—Influence of the Ovary.**—The basis for the study of gynecological pathology is an understanding of the changes which the endometrium undergoes during the menstrual cycle. Throughout the entire menstrual cycle of twenty-eight days the endometrium is responding to influences from the ovaries, so that the uterus may be said to be the mirror which reflects ovarian activity. If that activity becomes perverted, the changes in the endometrium will cross the boundary line between the physiological and the pathological.

In the human subject ovulation occurs at the middle of the menstrual cycle, on the thirteenth or fourteenth day from the beginning of the last period. Immediately after ovulation the corpus luteum begins to be formed from the stratum granulosum of the ruptured follicle. The ripening follicle produces one active principle which acts on the endometrium, while the corpus luteum produces quite a different principle with an effect opposite and antagonistic to the follicular one. As soon as the corpus luteum degenerates and becomes functionally impotent, which happens from twenty-four to thirty-six hours before menstruation, the follicular principle, which has been present all the time though suppressed, reasserts itself and continues to do so until the development of the next corpus luteum. It is this resumption of follicular activity which is probably the direct cause of menstruation. If the ovum continues to live on account of being fertilized, the corpus luteum will persist and grow larger, and the amenorrhea (absence of menstruation) of pregnancy is established. The follicular principle is called estrin or theelin, because when the fluid of ripening follicles is injected into an animal it brings on estrus or heat. In pregnancy there is a great overproduction of estrin, the excess appearing in the urine where it can readily be demonstrated. The corpus luteum hormone is called progesterin, because it stimulates premenstrual or pregestational changes in the uterus.

In order to test for the presence of estrin in follicular fluid, in the urine of pregnant animals, etc., a quantity of the fluid is injected into female mice which are either immature or have been castrated. In both cases estrus is produced within forty-eight hours, and is best demonstrated by observing the presence of squamous epithelium in vaginal smears, for one of the changes characteristic of estrus is cornification of the vaginal mucosa. The entire genital tract shares in these estrous changes, with the exception of the ovaries which are

unaffected. This is the method introduced by Frank and elaborated by Allen and Doisy. It must not be confused with the Aschheim-Zondek test for pregnancy.

**Influence of the Pituitary.**—Just as the endometrium seems to be under the influence of the ovary, so the ovary seems to be under the influence of the anterior lobe of the pituitary. (Fig. 331.) The periodicity of the ovary is not inherent in itself, but is dependent on the anterior pituitary which regulates it. The work of Smith and Engle, Zondek and Aschheim, and others, has shown that implants or extracts of the anterior lobe of the pituitary in an immature female animal

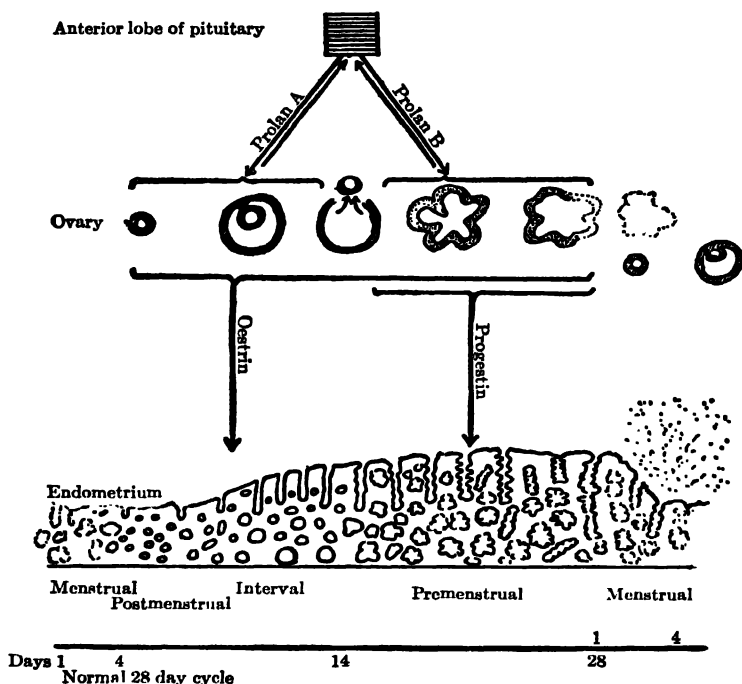


FIG. 331.--Diagram illustrating interrelationships between anterior pituitary, ovary and endometrium. (Jeffcoate.)

rapidly bring on a state of maturity or premature puberty. As a result of rapid maturation of the follicles, estrin is formed and this brings on all the phenomena of estrus. No changes are observed if the ovaries are first removed, for a castrated animal does not respond to anterior pituitary stimulation. In the literature on the subject the term female sex hormone often occurs. This is somewhat confusing, for it may include both the estrus-producing hormone of the ovary (estrin) and the ovary-stimulating hormone of the pituitary. In practice it is usually reserved for the former. It may be noted that estrin can be obtained from the male pituitary as powerful as that from the female.



**Influence of the Placenta.**—Extracts of placenta produce the same effect on the ovary as extracts of the anterior lobe of the pituitary, first stimulating the follicles and then causing luteinization. It is not possible to say with certainty if this hormone is produced by the pituitary and stored in the placenta or if it is produced by the placenta itself, but the latter alternative appears the more probable. (Collip.) During pregnancy there appears in the urine an ovary-stimulating principle, which is the active substance in the Aschheim-Zondek test for pregnancy, and which was formerly thought to be the pituitary hormone, the prolan of Zondek. It is now believed that no pituitary hormone appears in the urine, and that the effect is due to an anterior-pituitary-like substance produced by the placenta. These considerations do not, however, alter the great practical value of the test. In the original Aschheim-Zondek test the urine was injected into immature female mice, but in the more convenient Friedman modification adult female rabbits are used (the female rabbit ovulates normally only after mating). If the urine is from a pregnant woman, in the course of twenty-four to forty eight hours the ovaries will show hemorrhagic follicles (Fig. 332), or the even more significant crater from which the ovum is discharged before hemorrhage occurs into the follicle. After delivery the Aschheim-Zondek (or Friedman) test becomes negative in seven to ten days. If it remains positive it indicates retained placenta or the presence of hydatidiform mole or chorionepithelioma. It is positive in tubal pregnancy until tubal abortion destroys the chorionic villi in the tube.

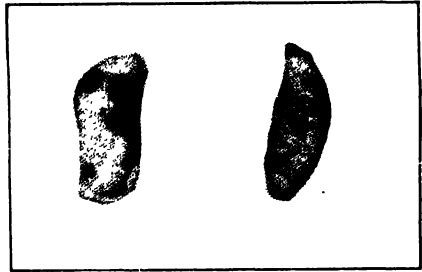


FIG. 332.—Friedman test. The ovary on the left shows hemorrhagic lesions which indicate a positive reaction; that on the right indicates a negative reaction.

It would appear that the placenta may produce (or store) three different principles: estrin, anterior-pituitary-like (A-P-L) principle (Collip), and emmenin (Collip). All of these appear in the urine during pregnancy, and they are probably all closely related chemically. *Estrin* is produced in such large amount during pregnancy and excreted in the urine that it seems unlikely that the bulk of it can be produced by the follicular tissue of the ovary. Estrin acts on the adult castrated animal with the production of estrus. When given by mouth it produces no effect on the immature animal. The *A-P-L principle* when injected into immature rats produces estrus, but not if the pituitary has first been removed; it evidently acts through the pituitary. It produces marked enlargement of the seminal vesicles and prostate in the male. *Emmenin* differs from the other two in that oral administration will bring on estrus in the immature animal. It produces no effect on the adult castrate.

**Endometrial Changes.**—The female sexual cycle can be divided into two phases: (1) a *proliferative, estrin or follicular phase* from the close of menstruation to ovulation (from about the fifth to the twelfth day), and

(2) a *secretory, progestin or lutein phase* from ovulation to about twenty-four hours before the onset of menstruation. We shall find that these two phases are accurately reflected in the ovarian mirror—the endometrium. (Figs. 333 and 334.) In the estrin phase there is repair of the tissues destroyed during menstruation; in the progestin phase the endometrium is prepared for an approaching pregnancy (decidual reaction, pseudopregnancy). If the ovum remains unfertilized, all sign of these preparations is removed in the destructive and hemorrhagic process of menstruation.



FIG. 333.—Estrin phase.



FIG. 334.—Progestin phase.  $\times 45$ .

Figs. 333 and 334.—Endometrial phases.

The *proliferative or estrin phase* of the menstrual cycle is of about one week's duration, extending from the end of menstruation to ovulation. It provides the histological picture of what used to be considered the normal endometrium. During this period the endometrium is being acted on by the estrin of the ripening follicle. It grows steadily in thickness, the low epithelium of the postmenstrual stage becomes tall and columnar, mitotic figures are numerous both in the glandular epithelium and the stroma, there may be a pseudostratification of the columnar epithelium which may be several layers thick in some of the glands, and the glands become more and more tortuous, particularly in the deeper part of the endometrium giving it a spongy appearance.

The *secretory* or *progestin phase* begins after ovulation and formation of the corpus luteum, but the changes are only well developed about five days before menstruation. This is the stage of glandular activity and secretion (not reproduction) and of decidual reaction. The secretory activity of the glands becomes more and more marked, the epithelium which is at first distended with mucin changes from high to low columnar and appears to melt into the mucin which passes into the lumen of the gland. As a result of this activity the glands develop a characteristic spirally twisted or corkscrew appearance, and in consequence buds project into the lumen like the teeth of a saw, giving a false suggestion of papillary formation. It is this highly glandular but perfectly normal appearance which in the past was responsible for the very common diagnosis of "glandular endometritis." By this time the endometrium is divided into a superficial compact layer and a deep spongy layer full of spiral glands. The stroma cells of the compact layer undergo the second change that is characteristic of the premenstrual or corpus luteum phase, the oval cells becoming enlarged, rounded, and epithelioid in type, and closely resembling the decidua cells of pregnancy. It is indeed a decidual reaction, for if pregnancy supervenes it is these cells which form the decidua of pregnancy. For this reason it is never safe in medico-legal work to make a diagnosis of pregnancy merely because decidual cells have been found in uterine scrapings. The decidual reaction has been called a pseudopregnancy. A day or two before menstruation the superficial layer is infiltrated with leucocytes. Widespread necrosis of the tissue on the surface now takes place, the compact layer is cast off, the walls of the capillaries are destroyed, and menstrual bleeding is the result. This necrosis and expulsion of tissue may be regarded as an expulsion or abortion of the pseudopregnancy. If impregnation has occurred and a fertilized ovum reaches the uterus, menstruation does not occur, the decidua-like layer is retained, and developed into the decidua of pregnancy.

It is evident that these endometrial changes are the combined result of the follicular hormone and the lutein hormone. If ovulation fails to occur and no corpus luteum is formed, only the first set of changes will take place. We shall see that this is of profound importance, and that it is one of the principal causes of idiopathic uterine hemorrhage.

### ENDOMETRIAL HYPERPLASIA AND FUNCTIONAL UTERINE HEMORRHAGE

Just before or during the menopause a woman may begin to suffer from irregular uterine hemorrhage, which may take the form either of profuse periodic bleeding or of prolonged and continuous bleeding. This irregular hemorrhage may occur at earlier age periods, and sometimes in young women. When the uterus is curetted the endometrium is found to be thick, sometimes it forms papillary excrescences on the surface, and microscopically it presents a markedly glandular appear-

ance. It is now known, thanks to the work of Schröder and many others, that the condition is due to ovarian dysfunction (pathological persistence of a ripening follicle), that there is no primary lesion in the uterus, and that the hemorrhage is really functional.

Menstruation is not necessarily dependent on ovulation. In the absence of ovulation there are no cyclic changes in the endometrium, no formation of a pseudopregnancy, but bleeding occurs just the same. In the condition under discussion the ovary shows two abnormalities. In addition to being somewhat atrophic, there is an entire absence of lutein tissue, but it does contain one or more ripening follicles. Apparently something prevents ovulation from occurring, and as no corpus luteum is formed the premenstrual changes in the endometrium do not occur. There is a continued overproduction of estrin by the persistent ripening follicle, and the endometrium shows the effect of this overstimulation by manifesting in pathological form the first or hyperplastic phase of the menstrual cycle. It is the absence of the normal secretory "topping-off" caused by progesterin which is responsible for the type of endometrium seen in functional hemorrhage. Injection of estrin into animals produces similar changes in the endometrium.

The *endometrium* is markedly thickened, and may measure 15 mm. Sometimes it shows polypoidal protrusions on the surface. *Microscopically* the endometrium presents a highly glandular appearance. The arrangement of the glands is disorderly as compared with the normal vertical extension from base to surface, they are increased in number, there is great variation in size and shape, and the epithelium may be several layers thick (pseudostratification). Some degree of adenomyosis is often present, *i. e.*, an invasion of the muscular wall by the glands of the endometrium; this is a minor form of true adenomyoma, which itself is a manifestation of endometriosis. Cystic dilatation of the glands in the deeper layers is common, so as to give what has come to be known as a "Swiss cheese appearance," and the condition has been called Swiss cheese hyperplasia. (Fig. 335.) The stroma cells show numerous mitoses, there is extremely marked vascular congestion and a good deal of edema. Decidual reaction is completely absent. If bleeding is going on when the curettage is done, two additional changes will be observed: (1) necrosis of the superficial layers and thrombosis of the small vessels; (2) extensive infiltration with polymorphonuclear leucocytes and mononuclears, but no plasma cells. The necrosis is patchy, not diffuse as in true menstruation. The two most characteristic features of the microscopic picture are the cystic glands and the patchy necrosis of the surface. The hemorrhage is due chiefly to the local necrosis, but the cause of the necrosis is uncertain. It may be due to cessation of corpus luteum influence as in normal menstruation, or more probably to overstimulation which may lead to thrombosis. To choose a suitable name for the condition is difficult. From the physiological viewpoint it may be called "hyperestrinism," or from the morphological viewpoint "cystic glandular

hyperplasia of the endometrium." Its great importance lies in the fact that it is the chief cause of functional uterine hemorrhage. The ovaries commonly present many small follicular cysts and a complete absence of lutein tissue, this being the morphological basis of the hyperestrinism. For this reason the administration of A-P-L hormone, which is luteinizing in its effect, is frequently of value in this condition.

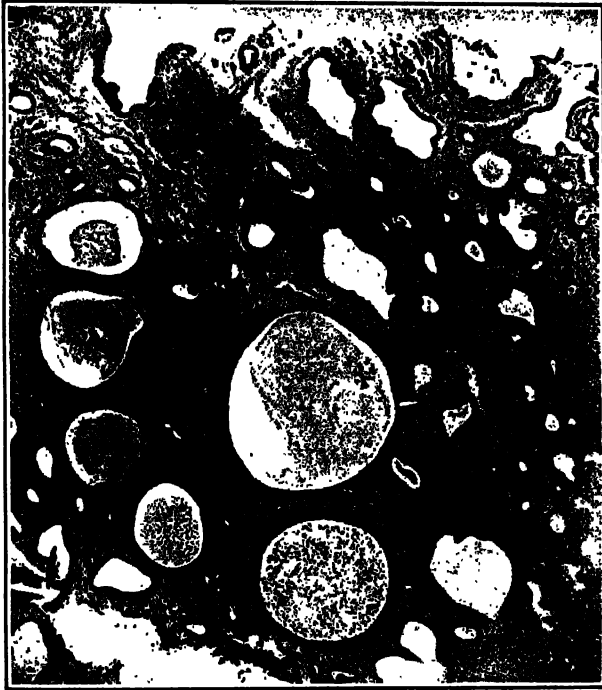


FIG. 335. --"Swiss cheese hyperplasia" of endometrium with marked glandular formation.  $\times 18$ .

*Corpus luteum overactivity* is the converse of the condition just described. The endometrium shows excessive lutein phase changes, even a few days after the middle of the menstrual cycle, and the condition may resemble that of early pregnancy. In these cases the ovaries contain large corpora lutea or excess of lutein tissue. These changes observed in the human subject correspond with the experimental observations of Burch, Williams and Cunningham, who found that the injection of estrin or corpus luteum extract in animals produced corresponding changes in the endometrium.

### ENDOMETRITIS

Acute inflammation of the endometrium may affect the pregnant or non-pregnant uterus. The latter is relatively unimportant. It is

commonly caused by the gonococcus, but gonorrhea is chiefly a disease of the cervix, and the infection may pass from there to the tubes producing very little change in the body of the uterus. In acute fevers there may occasionally be an acute endometritis (blood infection), and when the cervical canal is closed by carcinoma the body of the uterus may be distended with pus, a condition of pyometra. Of far greater importance is puerperal endometritis, or acute inflammation of the pregnant uterus during the puerperium.

**Puerperal Endometritis.**—The normal uterus is resistant to infection, but the puerperal uterus is highly susceptible, for the interior presents a raw surface much traumatized and often containing portions of placental tissue separated from their blood supply. Secondary factors such as exhaustion, instrumental interference, hemorrhage, etc., predispose to infection. But the primary cause is the bacteria which gain access to the uterus. There are three main methods of infection: (1) germs introduced from without, usually by attendants; (2) germs present in the vaginal canal; (3) autogenous infection from an extra-genital source in the patient herself, usually the nose and throat. In the great majority of cases streptococci are the infecting germs. These may be aerobic or anaerobic. Most of the severe infections are due to *aerobic hemolytic streptococci*. Lancefield and Hare, by means of precipitin tests have divided hemolytic streptococci into four groups, A, B, C, and D, of which only Group A is responsible for human infection. Fully two-thirds of the hemolytic streptococci occurring in the nose and throat are harmless for man, not being in Group A, an important point to remember in looking for the source of infection in an outbreak of puerperal sepsis in a hospital. Group A is found in the vagina in puerperal sepsis and in the throats of carriers or of the patient herself. Thus the human nasopharynx is the main reservoir of the A strain in Nature, the germs being transmitted by various means to the parturient canal. It was in 1910 that Schottmüller first called attention to *anaerobic streptococci* as a frequent cause of puerperal sepsis, but it is only very recently that this truth has been generally accepted. The great majority of mild cases are caused by these organisms. The infection is of a less severe type, less likely to prove fatal, as anaerobic streptococci are generally non-invasive saprophytes, but under favorable conditions such as the presence of thrombi in the uterine veins they may reach the blood stream with fatal results. It is an endogenous infection, as the germs are in the vagina of a large percentage of women at term. Its control presents therefore a more difficult problem than exogenous infection, but it may be combated by the vaginal instillation of antiseptics. It is evident that in anaerobic infections the streptococci will be found in smears but not in ordinary cultures unless anaerobic methods are used.

The uterus is soft, flabby, and enlarged because normal involution is prevented. The cavity is lined by dirty, breaking-down, necrotic material, under which there is a protective zone of leucocytes. When the infection is mild this zone is wide, and discharge of the infected

material is followed by recovery, for blood invasion has not occurred. In the severe streptococcal infections, the leucocytic zone is thin, and the organisms are seen spreading into the deeper parts of the uterine wall. They may reach the serous coat and set up peritonitis, they may pass along the Fallopian tubes and flood the general peritoneal cavity, or they may spread throughout the body by the blood stream. The large venous sinuses are filled with septic thrombi, which break down and pass into the circulation as septic emboli, setting up pyemic abscesses in the lungs. The blood infection is also responsible for abscesses in the kidneys, joints, etc. An acute endocarditis is a frequent complication. Blood culture is often positive owing to the severe septicemia.

**Endocervicitis: "Cervical Erosion."**—The endometrium of the body of the uterus does not provide a favorable nidus for chronic infection on account of its simple glandular structure and the fact that in large measure it is renewed every month. The reverse is true of the cervix. Here there are no menstrual changes, and the complex racemose glands may harbor infecting microorganisms for long periods. Chronic inflammation of the cervix is accordingly the commonest of all gynecological lesions. By far the commonest cause is laceration of the cervix at childbirth, followed by pyogenic infection. The usual infecting organisms are staphylococci, streptococci, and *Bacillus coli*. Gonorrheal infection of the cervix is the second common cause, but it is of minor importance compared with the first. The gonococcus may infect a laceration, or it may cause infection in a nullipara, as the gonococcus can readily penetrate intact columnar epithelium. The following description applies to the cases which follow laceration.

The infecting bacteria gain entrance to the racemose glands which arise from the columnar epithelium of the cervical canal and penetrate the depths of the muscle. These glands are not seen in the vaginal portion of the cervix which is covered by stratified squamous epithelium. The glands are irritated as the result of the infection, and pour out the thick, viscous, mucopurulent secretion which is characteristic of leucorrhea. It may be said that leucorrhea is almost always a sign of cervicitis. The stroma of the endometrium shows edema, and an infiltration with lymphocytes and plasma cells, the latter being the most characteristic cells of chronic inflammation in the female genital tract. In time the inflammation extends to the fibromuscular layer, so that the condition becomes a true cervicitis and not merely an endocervicitis. The columnar epithelium of the surface is curiously resistant and is not desquamated.

Owing to the constant irritation of the infected leucorrheal discharge or for some other reason at present unknown, a patch of squamous epithelium at the external os undergoes maceration and becomes separated, leaving a raw surface which partially or completely surrounds the os. The raw surface is quickly covered by an outgrowth of the columnar epithelium of the cervical canal. The covered patch remains red, however, for the underlying vascular tissue shines through

the thin layer of epithelium. This is the condition which has been known in the past as "cervical erosion," a mere clinical nickname for the raspberry red appearance of what used to be thought was a true granulating ulcerated surface. If the cervix has been badly lacerated the os may become everted and patulous. The new epithelium appears to be stimulated by the constant irritation, and gives rise to new racemose glands in the portio vaginalis. This gland formation may be very marked, so that the condition has been called a proliferative adenoma, and may give to the surface a nodular appearance. In course of time the inflammation dies down, and as a sign of healing the squamous epithelioma once more replaces the columnar type over the disputed patch, either by growing under it from the



FIG. 336.—Endocervicitis with marked glandular proliferation and Nabothian follicles.  
X 16.

edge or by a conversion of the columnar into the squamous stratified type. The new epithelium tends to close the mouths of the ducts of the new glands, and these may undergo cystic dilatations so as to form the bluish swellings on the portio vaginalis known as *Nabothian follicles*. (Fig. 336.) In some cases the squamous epithelium may grow down into the ducts, forming epithelial plugs which may be mistaken for commencing carcinoma. In the deeper parts of the cervix there is fibrosis and scarring, so that the cervix becomes hard, and owing to contraction of the scar tissue there may be marked eversion of the os.

**Pelvic Cellulitis (Parametritis).**—This is a term commonly used by gynecologists. Cellulitis signifies an inflammation of connective tissue due to a wound infection. Pelvic cellulitis may result from infection of lacerations of cervix



and vagina occurring during parturition or abortion, or from surgical operations on the cervix. It frequently occurs in conjunction with carcinoma of the cervix. Infection reaches the pelvic cellular tissue either by lymphatics or direct continuity of tissue. The common infecting organism is the streptococcus. Infection spreads in the retroperitoneal fascial planes and there may be abscess formation. While the condition may be a long drawn out one, resolution is usually complete and no impairment of reproductive function results.

### SYPHILIS OF THE UTERUS

The cervix is the only part of the uterus affected by syphilis. The lesion may be primary, secondary or tertiary. The primary lesion is a chancre, which can only be diagnosed with certainty by finding the *Spirochæta pallida* with the dark-field method. Many cervical chancres have been diagnosed clinically as carcinoma. The secondary lesion is a mucous patch. The tertiary lesion is a gumma, which may also be mistaken clinically for carcinoma, but can easily be distinguished from it in microscopic sections. All of these conditions are uncommon.

### ENDOMETRIOSIS

This conveniently non-committal term is used to denote a condition characterized by the formation of endometrium-like masses in a variety of places in the female pelvis and abdominal cavity. As the masses may resemble tumors they are known as endometriomata. The origin of these lesions is a matter of dispute.

It was Sampson of Albany who in 1921 was the first to direct attention to that manifestation of endometriosis which he called endometrial implants. The occurrence of so-called chocolate-colored cysts of the ovary had long been recognized, and lesions of similar structure were found in the rectovaginal septum and other parts of the pelvis. Sampson suggested that these lesions were due to implantation of living endometrial cells on the surface of the ovary, peritoneum, etc. These cells were supposed to be cast into the cavity of the uterus during menstruation, pass along the tubes, and finally settle and grow at the site of the future lesion. The "implant" consists of gland-like spaces surrounded by columnar epithelium, and separated by the cellular stroma characteristic of the endometrium. Hemorrhage occurs at each menstrual period, so that the lesion contains either fresh blood or blood pigment. When the ovarian cyst ruptures the contents are scattered throughout the pelvis together with more desquamated endometrial cells which set up secondary endometrial implants.

Jacobsen's experimental work served to support Sampson's theory. Uterine curettings from rabbits in heat were sowed in the abdominal cavity, and implants were formed in 83 per cent of the animals. Similar results were obtained in monkeys, the implants being identical with those seen in the human patient.

Sampson's views have met both with support and opposition, the latter especially in Germany, where R. Mayer's theory of the serosal origin of the supposed implants is the popular one. The serosal theory, with which the writer is in agreement, is based on the fact that the entire epithelial apparatus of the female genital tract (endometrium, germinal epithelium of the surface of the ovary, etc.) is

derived originally from the primitive peritoneum which forms the epithelial lining of the celomic cavity. As the result of ovarian hormonal stimulus the serosa is believed to revert to its original function and form epithelium-lined cavities. Every pathologist is familiar with the fact that as the result of some stimulus such as chronic irritation the flattened serosal cells in either sex may become cuboidal, invade the underlying tissue, and surround gland-like spaces.

The question of ectopic decidual reaction is of interest in this connection (Weller). A nodular decidual reaction in the subserosa of the appendix is common during pregnancy. Similar lesions are found on the ovary, tube, broad ligament, rectal wall, etc., *i. e.*, a similar distribution to endometriosis. On the appendix the nodules are often mistaken by the surgeon for tubercles. It is evident that under appropriate hormonal stimulation decidual elements may develop from the connective-tissue cells which lie under the serosal cells in the pelvis and lower abdomen. The mesothelial cells of the surface, especially when entrapped in adhesions, appear to form the epithelial elements of endometriosis. Excessive estrin stimulation of the mesothelial and connective tissue is probably responsible for at least many cases of endometriosis, just as it is probably responsible for fibroadenoma of the breast, adenomyoma of the uterus, and possibly uterine fibroids. It may be noted that in all these conditions sterility and uterine hemorrhage are commonly associated features.

The older view that the chocolate-colored blood cysts of the ovary are follicular in origin has been revived by King. It has long been known that some cysts derived from the Graafian follicles, and especially from atretic follicles, may be lined by epithelium which cannot be distinguished from that of the endometrium. This is only natural, as the epithelium of both organs has a common developmental origin. Rupture of a chocolate-colored cyst may be followed by implants on the peritoneum. It is important to realize that the idea of normal adult tissues becoming implanted in other organs and growing there so as to produce irritation is quite without precedent in the science of pathology. Finally it must be recalled that transplantation is not necessary to account for the presence of a tissue at a distance from the normal site of that tissue. Metaplasia will give the same result.

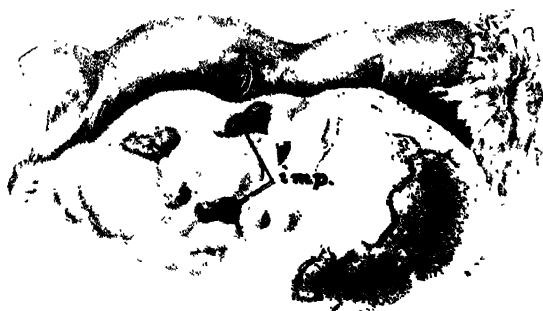
These objections are raised not with the idea of discrediting Sampson's theory and the brilliant work by which it has been supported, but in order to bring home the truth that it is still a theory, and not a fact as many gynecologists seem to imagine. It is possible that some of the lesions may be endometrial in origin, some serosal, and some ovarian.

The occurrence of the lesions is confined to the active reproductive period of the patient's life. Removal of the ovaries may be followed by atrophy and disappearance of the lesions. They are said occasionally to undergo malignant change, and Sampson believes that some of the malignant cystadenomas of the ovary arise in this way.

The *lesions* are most often seen in the *ovary*, where they form one

## PLATE XVIII

FIG. 1



**Endometriosis (Chocolate-colored Cysts) on Surface of Ovary.**

(John A. Sampson, Surg., Gynec. and Obst., March, 1924.)

FIG. 2



**Endometriosis of Terminal Loop of Ileum.**

(John A. Sampson, Surg., Gynec. and Obst., March, 1924.)



variety of ovarian hematoma, and are commonly known as *chocolate-colored cysts* (Plate XVIII, Fig. 1). The cysts, which are close to the surface, are quite small, are lined by columnar epithelium, and separated from one another by the highly cellular stroma so characteristic of the endometrium, in which are embedded many small glands like those of the uterus. There is no plain muscle in the ovary, but in the other lesions this is commonly present. The contents are hemorrhagic, and the blood is renewed at each menstrual period. Rupture of the cysts and liberation of the blood may be followed by the formation of peculiarly dense adhesions which in the past have been naturally thought to be inflammatory in nature.

Similar lesions may occur in the rectovaginal septum. The dense and hard adhesions may be mistaken for a malignant growth in this region. Endometriomata may occur in the Fallopian tubes, the broad and round ligaments, the appendix, the wall of the intestine (Plate XVIII, Fig. 2), the umbilicus, the groin and in abdominal scars after operations on the uterus. Blood may be discharged from an umbilical endometrioma at the menstrual period. Endometrioma of the groin is particularly puzzling. Here the mechanism cannot be that of endometrial implantation. Sampson has shown that endometrial tissue may be found within lymphatics and venous sinuses, and suggests that the cellular masses may spread in the same way as carcinoma, *i. e.*, by the lymph and blood stream as well as by the natural passages (tubes). An inguinal endometrioma may therefore be due to lymph spread. Or it may arise from the remains of an embryological peritoneal process in the inguinal canal, the processus vaginalis (serosal origin).

### TUMORS OF THE UTERUS

**Fibromyoma.**—The tumor known as myoma, fibromyoma and fibroid tumor of the uterus is the commonest of all neoplasms. It is even more frequent in colored than in white women. Although not strictly accurate the condition is commonly called a *fibroid*. The tumors are confined to the reproductive period of life. This suggests that they may bear some relation to ovarian activity. The ovaries are often enlarged, and contain cysts and large unruptured follicles. In the breast the common fibroadenoma, which is often more of a fibroma, is most probably due to abnormal ovarian stimulation. The same may be true of the fibromyomas of the uterus. They never appear after the menopause, and usually tend to retrogress in that period. When estrogenic hormone is introduced under the skin of a guinea-pig in tablet form, uterine fibromyomata are produced; these cease to grow and retrogress when the hormone ceases to act. The tumors occur chiefly in the body of the uterus. Cervical tumors are relatively uncommon.

In its *gross appearance* the fibroid tumor varies considerably. There may be a single tumor or large numbers; they may be very small or

very large, and their consistence may be much changed by degeneration. As a rule, the tumor is hard, circumscribed, and the cut surface presents a whorled appearance, due to interlacing bundles being cut in different planes. The more fibrous tissue it contains, the harder and whiter it is, contrasting with the relatively soft and brownish-red surrounding muscle. (Fig. 337.) As it grows expansively it compresses the muscle and thus forms for itself a capsule from which it can often be shelled out. According to its site the tumor is divided into interstitial, submucous, and subperitoneal varieties. The *interstitial* is the common form, for every fibromyoma commences in the substance of the muscle. It is well supplied with blood from the surrounding muscle, so that degeneration is not very common in



FIG. 337.—Fibromyomata of uterus. The white color is due to the large amount of fibrous tissue.

this form. The *submucous* fibroid is formed by the centripetal growth of an interstitial tumor. It projects into the uterine cavity, and, owing to the uterine contractions it may become more and more polypoid, until finally it may appear in the vagina. Even when quite small it may cause marked uterine hemorrhage owing to the irritation of the endometrium which it produces. The overlying endometrium may be remarkably thickened. A large tumor may distend the uterine cavity, giving an appearance which may so closely simulate pregnancy that a correct diagnosis may be impossible even when the abdomen has been opened. In rare cases the cavity of the uterus may be covered with small tumors. The *subperitoneal* fibroid is centrifugal in growth, so that it becomes subserous and may be pedunculated. *Twisting of the pedicle* may interfere with the blood supply, so that

degenerations are most common in this form. In rare cases the tumor may become adherent to the omentum and derive its chief blood supply from that source (parasitic fibroid). The subperitoneal tumors are usually multiple and may attain an enormous size. It is common to find two or all three varieties present in the same uterus.

The *microscopic appearance* is a mixture of plain muscle and fibrous tissue in varying proportions. The muscle fibers run in interlacing bundles, some of which are cut longitudinally, some transversely. (Fig. 338.) The small tumors consist mostly of muscle, but as they grow in size the proportion of fibrous tissue becomes greater, and tumors of long standing may be almost entirely fibrous. The nuclei of the muscle fibers are short, plump, and fusiform, while those of the fibroblasts are longer, slender, and curved.



FIG. 338. —Myoma of uterus. The fibers run in interlacing bundles.  $\times 225$ .

*Cervical fibroids, i. e.*, tumors originating in the cervix, are not common, although fibroids of the body may invade the cervix. A true cervical fibroid is single. As it grows in size the uterus becomes perched on the summit of the tumor, and if the patient becomes pregnant normal delivery is impossible.

*Degenerations.*—The blood supply of a fibroid is easily interfered with, so that degenerations are common. The subperitoneal form is nourished solely through its pedicle, and it is in this variety that degeneration is most frequent. *Atrophy* may occur after the menopause, due probably to loss of the ovarian stimulus, and a similar result may follow removal of the ovaries. *Hyaline degeneration* is the commonest change, and is due to an insufficient blood supply. The fibrous tissue becomes hyaline, and the muscle fibers tend to disappear. *Cystic degeneration* may follow the hyaline change. The hyaline material becomes liquefied, and cyst-like spaces are formed, but they have no epithelial lining. *Fatty degeneration* is seen in old fibroids. The cut surface is yellow and homogeneous, and the muscle fibers contain fat droplets which can be demonstrated by means of the special stains for

fat. *Calcification* may be a sequel to fatty degeneration, and is seen in the subserous fibroids of elderly women. The entire tumor may become converted into a mass of stone, which forms a striking feature in the roentgen-ray picture, but gives rise to no special symptoms. *Red degeneration* is a peculiar change usually associated with pregnancy, and marked by sudden pain and tenderness in the tumor. The latter becomes quite soft and of a bright red color like that of raw beef (Plate XIX). The red color is due to a collection of blood in the tissue which becomes hemolyzed and causes diffuse staining of the entire tumor. The condition is probably the result of thrombosis of the veins, so that it may be regarded as a red infarct. The venous obstruction, usually occurring as it does in pregnancy, may be attributed to pressure, contractions of the uterus, or torsion of the tumor. The change is commonest in the interstitial variety. *Sarcomatous degeneration* of a myoma is discussed in connection with Sarcoma of the Uterus.

**Adenomyosis.**—In this condition there is an intermingling of glandular and muscular elements. It is not a true tumor, so that the term adenomyoma, formerly applied to it, is a misnomer. Von Recklinghausen believed that the epithelial elements of the lesion arose from portions of the Wolffian body which had become separated in early fetal life, but Cullen showed by means of serial sections that there was direct continuity of epithelium between the lesion and the endometrium. Areas of decidua have been found in the lesion shortly after labor, and even in cases of tubal pregnancy. Although the lesion is sometimes spoken of as a variety of endometriosis, it will be apparent that the relation of the two conditions is merely casual and in no way intimate. Adenomyosis consists of and is derived from endometrium, but in endometriosis the new tissue is more probably of serosal origin.

The *gross appearance* is usually characteristic. The lesion may be limited to the anterior or posterior wall or may form a mantle just outside the mucosa. Although the uterus may be enlarged to two or three times its normal size, and the affected part may be markedly thickened, the normal outline of the organ is usually retained. When the uterus is opened the diagnosis can often be made from the gross appearance. The anterior or posterior wall is diffusely thickened, with a complete absence of the sharp demarcation so characteristic of the ordinary fibroid. The thickened portion of muscle is coarsely striated, and homogeneous translucent areas resembling mucous membrane may be scattered through it. These areas often present a brownish discoloration due to the presence of extravasated menstrual blood. Small cystic spaces filled with chocolate-colored contents may be scattered throughout these mucosal areas. The line of demarcation between the lesion and the normal mucous membrane is always sharp; it extends to, but never into, the endometrium.

*Microscopically*, the growth is made up of fibromyomatous tissue, only differing from that of an ordinary fibroid in that it is not encapsulated, together with glandular structures. The latter resemble the normal endometrium, although not so regular in appearance (Fig.



PLATE XIX



Red Degeneration of Uterine Fibroid



339). "The uterine mucosa is often of normal thickness and looks perfectly normal, but as we approach the underlying diffuse myomatous tissue the mucosa is seen to penetrate it in all directions, sometimes as an individual gland, but often large areas of mucosa are seen extending into the depth. In favorable sections one can follow a prolongation of the mucosa half way through the uterus" (Cullen).

**Interstitial Endometrioma.**—

In endometriosis the dominant element is epithelium. Occasionally the interstitial cells of the endometrium assume invasive qualities under the influence, apparently of hormonal stimulation. Under normal conditions root-like strands of these cells penetrate for a short distance into the muscularis. As the result of abnormal stimulation this invasion may become almost sarcomatoid in its character and form a tumor-like lesion known as interstitial endometrioma (Goodall). The interstitial cell is in a constant state of flux during the sex life of the individual, and it has a high potentiality for differentiation, so that the mass may resemble a sarcoma (soft) or fibroma (hard) in both gross and microscopic appearance. Undoubtedly in the past this condition has frequently been diagnosed pathologically as sarcoma. An unique feature presented by some of these tumors is the presence on the cut surface of hundreds of worm-like masses occupying either lymphatics or veins. In one case with which I am familiar the patient is alive and well four years after removal of the uterus, although long strings composed of masses of interstitial endometrial cells could be pulled out of the veins of the uterine wall.

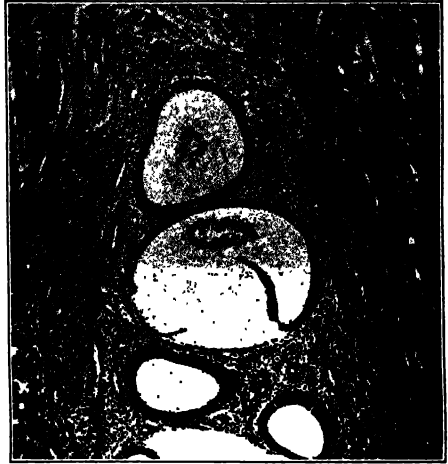


FIG. 339.—Adenomyosis of the uterus. Deep in the wall of the uterus there are dilated endometrial glands surrounded by the cellular stroma of the endometrium.

**Carcinoma of the Cervix.**—Cancer of the uterus is one of the commonest forms of cancer, and cancer of the cervix is much more common than cancer of the body. The two forms are so different in their behavior that they may be regarded as different diseases. Uterine cancer is much less common in Jewesses than in any other race. Over 90 per cent of cases occur in women who have borne children, and it is noteworthy that the fecundity of patients who eventually develop this form of cancer is above the average. Laceration of the cervix is a frequent antecedent. These facts form the basis for the confident assertion that injury to the cervix is the most important etiological factor. Although this dogma has been accepted for many years, it seems time to call it in question. In no other part of the body does a single laceration, even though followed by infection, act as a carcinogenic agent. It is now known that the epithelium of the cervix

is subject to hormonal stimulation, and it is possible that this may be a factor of greater importance than trauma (Hofbauer). The prolonged administration of estrin produces cancer of the cervix in the mouse, an animal in which this form of cancer is unknown as a spontaneous disease (Gardner, *et al.*). It may be noted that cancer of the cervix occurs only in those mice which have shown themselves to be resistant to mammary cancer or in whom this form of cancer has been removed surgically. The highest incidence of female genital cancer occurs at or after the menopause when ovulation has stopped. There is, therefore, no corpus luteum hormone, but the output of estrogen may continue, especially if the ovaries are cystic. Carcinoma of the cervix may occur in women who have been delivered by Caesarian section, and in whom there can be no question of laceration of the cervix. In one case with which I am familiar carcinoma developed ten years after delivery by section. It is evident that hormonal imbalance must be considered as a possible agent in the etiology of female genital cancer.

The *gross appearance* may take a papillary form or an infiltrating form. (1) The *papillary variety* forms a large fungating mass, projecting into the cavity of the vagina, and appearing to arise from the lip of the external os. There is little tendency to invasion of the deeper tissues, and as hemorrhage, especially after coitus, is an early symptom, diagnosis may be made fairly early, so that the prognosis is less unfavorable. (2) The *infiltrating variety* (Fig. 340), which is the common one, may give little sign of a tumor on the surface, but extends deeply in the direction of the internal os, causing enlargement and hardening of the cervix, but unaccompanied by symptoms for a considerable time. In the course of time there is extensive necrosis and sloughing, with destruction of the cervix and the formation of a ragged, badly infected cavity. (Fig. 341.) Sometimes the cervical canal becomes blocked by the tumor, so that drainage from the uterine cavity is impossible and pus accumulates, often under very high pressure, a condition known as pyometra. A similar state of affairs may be produced by fibrosis and cicatricial contraction of the canal caused by treatment (often cure) of the tumor by radium. When the cervix is painted with Lugol's solution the normal epithelium is colored a deep brown by the iodine (glycogen reaction), while diseased epithelium and cancer is unstained. This is used as a guide for the site of biopsy in early cancer (Schiller test), but unfortunately cervical erosion also remains unstained.

The *microscopic appearance* has caused most of the difficulties of classification. Two types of epithelium are found in the cervix. The vaginal portion (portio vaginalis or simply portio) is covered by stratified squamous epithelium of the epidermal type, while the cervical canal is lined by a single layer of columnar epithelium. Corresponding to these two types of epithelium we find two types of tumor, a common epidermoid carcinoma, and a rarer adenocarcinoma which forms less than 4 per cent of the total. But it is not safe to conclude that the former must arise from the portio and the latter from the

cervical canal, for squamous epithelium may extend into the canal, and the racemose glands of the portio may be the starting-point of an adenocarcinoma. It seems probable that in the majority of cases the tumor originates at the external os which has been the seat of a cervical erosion with change from a squamous to a columnar type of epithelium and reversion again to a squamous type with gradual development of an epidermoid carcinoma. Columns of cells grow down into the deeper tissues, usually showing numerous mitotic figures.

Gynecologists have made minute subdivisions according to the type of cell (spinous, transitional, spindle, etc.) in the hope that the radio-sensitivity of the tumors might be determined, seeing that radiation



FIG. 340.—Infiltrating carcinoma of the cervix uteri.



FIG. 341.—Carcinoma of cervix. The cervix is converted into a ragged fungating mass.

therapy plays such an important part in the treatment of the condition. It seems better to speak merely of the degree of differentiation which the tumor exhibits. The cases of epidermoid carcinoma may be divided into three groups according to their degree of differentiation, and these groups show a corresponding variation in degree of radio-sensitivity (Healy and Cutler). Group 1 (20 per cent) is the *adult type*, made up of highly differentiated cells with a tendency to cornification and the formation of pearls. It is radio-resistant. Group 2 (60 per cent) is the *plexiform type* in which the cells have lost most of their squamous character, show a plexiform arrangement, a tendency to infiltration, and a moderate degree of anaplasia. (Fig. 342.) The tumor is more radio-sensitive. Group 3 (20 per cent) is the *anaplastic type* in which the cells have lost all squamous characters, are completely undifferentiated and diffusely invasive. They are highly radio-sensitive. When the results of radiation therapy are analyzed the

curious position is revealed that the best results (permanent cure) are obtained with the most malignant tumors, *i. e.*, those of Group 3. The reverse is the case when the growths are removed surgically. The rather uncommon adenocarcinoma seems to be less invasive than the epidermoid form, so that the operative results are more favorable, but it is less radio-sensitive.



FIG. 342.—Carcinoma of cervix. The plexiform arrangement of the epidermoid cells is well shown.  $\times 115$ .

The method of diagnosing uterine cancer by examining the cells of a vaginal smear, first suggested by Papanicolaou in 1928, is claiming increasing attention. In 127 cases of cervical cancer a correct diagnosis by vaginal smear was made in 123 (Papanicolaou and Traut). The material is aspirated, blown on to a slide, fixed before being allowed to dry, and stained. A positive result indicates that a confirmatory biopsy should be performed. In cervical cancer abnormal cells are found in the smear showing great variety of form and size, atypical structure of their nuclei, and vacuolization of the cytoplasm.

**Spread.**—Spread may occur by permeation, by the lymph vessels, or by the blood stream. *Permeation* may carry the tumor cells outward to the parametrium, forward to the bladder, backward to the rectum, and downward to the vagina. It is very seldom that the tumor spreads so as to invade the body of the uterus, although the entire cervix may be involved. Obstruction of the ureters is common, causing an ascending infection which may prove fatal. *Lymphatic spread* leads to involvement of the iliac, hypogastric and sacral groups of lymph nodes. The tumor generally metastasizes late; only about 50 per cent of autopsy cases show gross metastases, and in radical hysterectomies lymph-node involvement averages about 30 per cent.

Cullen found malignant nodes in only 2 per cent of cases where the disease was still confined to the uterus. *Blood spread* is not common and is only found in advanced cases, in accordance with the rule that epidermoid carcinoma does not tend to invade the bloodvessels.

**Carcinoma of the Body of the Uterus.**—Cancer of the body of the uterus is much less common than cancer of the cervix, constituting only 10 per cent of the cases of uterine carcinoma. It occurs later in life, usually after the menopause, so that irregular bleeding is more likely to cause alarm. It is much less infiltrative than cervical carcinoma. For these reasons the prognosis is more favorable. Child-bearing is not an etiological factor, for it is even more common in nulliparæ than multiparæ.



FIG. 343.—Carcinoma of the body of the uterus. The uterus is bicornuate, and the carcinoma fills the cavity of both horns.

The tumor usually begins in the endometrium of the fundus and spreads superficially so that a large surface may be involved. (Fig. 343.) It assumes the papillary rather than the infiltrating form, and may constitute a mass which occupies the greater part of the uterine cavity, and causes a moderate degree of enlargement of the organ. Involvement of the cervix is very rare. Invasion of the muscular wall occurs in time, so that care must be exercised in performing a diagnostic curettage to avoid perforating the uterus, but there is never the early involvement of the parametrium which is so characteristic of cancer

of the cervix. Curettage gives definite chunks of cancer tissue; if the scrapings are scanty, soft and pink they are almost certain not to be malignant.

*Microscopically*, the picture is usually that of a typical adenocarcinoma with irregular malignant tubules invading the underlying muscle. Sometimes the structure is more anaplastic with little glandular formation. Diagnosis from fragments of scrapings is not always easy unless some muscle is included, for the new-formed glands may resemble those of endometrial hyperplasia. Attention must be paid to irregularity of staining, mitoses and evidence of invasion. Generally speaking the cytological rather than the histological features are those which count. When the pathologist is in doubt, it is generally not cancer. Histological grading of biopsy material is singularly disappointing and of little prognostic value, as different blocks may show widely varying pictures. Occasionally the carcinoma may be epidermoid in type. In rare cases the tumor may take the form of adeno-acanthoma, *i. e.*, a combination of glandular and epidermoid carcinoma.

**Spread.**—Spread takes place through the muscular wall, with eventual perforation. Fragments of tumor may be carried through the Fallopian tubes and infect the ovaries, so that the ovaries must always be removed together with the uterus. Lymph spread to the para-vertebral glands and blood spread to lungs and liver occur in the later stages.

**Sarcoma.**—Sarcoma of the uterus is an uncommon tumor. It usually occurs as a malignant change in a myoma, so that it may be called a myosarcoma or malignant myoma. Occasionally it may arise from the normal uterine wall. The *gross appearance* is characteristic, for the whorled or striated appearance of the fibroid is lost, the cut surface is homogeneous and brain-like, and the tumor is soft and may be of a yellowish color. Cyst formation and hemorrhage are frequent. *Microscopically* the tumor is composed of large fusiform cells, in many of which the nuclei are remarkably large and may show numerous mitoses. It is almost impossible to be certain if these cells are derived from pain muscle or from fibroblasts.

**Endometrial Sarcoma** is usually circumscribed but may be diffuse. It originates in the fundus, and often forms a polypoid bulky mass in which necrosis may occur as well as cystic areas of hemorrhage. *Microscopically* it consists of a mixture of fusiform and large spherical cells. The degree of mitosis parallels the clinical malignancy of the tumor. Invasion of the uterine muscle occurs, and spreads to peritoneum, regional lymph nodes and distant organs.

**Embryonal Tumors.**—These are very rare tumors containing a variety of tissues of mesodermal origin, of which striated muscle is the chief. The general structure is sarcomatous and they are usually called sarcomas or rhabdomyomas. The best-defined variety is the so-called *grape-like sarcoma* of the cervix or vagina, which usually occurs in young children, and projects into the vagina in polypoid masses that may become so edematous as to resemble a bunch of grapes. Most of the cells are round or fusiform, but striated muscle is usually present. The tumor is very malignant, and spreads both locally and by the blood stream.

**Chorionepithelioma.**—This highly malignant tumor, which arises from fetal and not maternal tissue, usually follows an abortion, some-



times is the result of a full-term pregnancy, and in rare cases has been found in the ovary and in the testicle. In about 30 per cent of the cases it is preceded by a hydatidiform mole, a benign epithelial tumor of the chorionic villi which will be described in connection with the pathology of the placenta. It is said that about 15 per cent of hydatidiform moles may show this malignant change, but it is impossible to get accurate figures, and this proportion is probably much too high. Both chorion-epithelioma and hydatidiform mole are often associated with an unusually large corpus luteum or bilateral lutein cysts. The connection is not certain, but it is probable that they are a result rather than a cause of the uterine condition. The tumor may develop very soon after pregnancy, or there may be an interval of months or years. The Aschheim-Zondek test for pregnancy is markedly positive. (See Hydatidiform Mole.)

The tumor commences at the placental site, usually in the fundus of the uterus. It forms a soft, red, highly hemorrhagic mass which projects into the cavity and at the same time invades the muscular wall. Secondary growths may be formed in the lower part of the uterus and in the vaginal wall; in the latter position the progress of the disease can be watched and the effect of treatment noted. Later the tumor appears on the outer surface of the uterus.



FIG. 344.—Chorionepithelioma consisting of clear Langhans' cells and dark syncytial masses.  $\times 350$ .

*Microscopically* the chorionepithelioma is an exaggeration of the condition normally found in pregnancy. The fetal part of the placenta consists of the chorionic villi, and the essential part of the villus is the trophoblast, the function of which is to invade the maternal blood sinuses. The trophoblast presents two types of epithelium, an inner layer of clear cubical cells with large pale nuclei known as Langhans' cells, and an outer layer of large dark multinucleated masses of cytoplasm known as the syncytial cells. The chorionepithelioma consists

mainly of clear Langhans' cells with a varying proportion of dark syncytial masses lying in large pools of blood. (Fig. 344.) The normal relationship of the two types of cell is lost, for the exuberant Langhans' cells have burst through the outer syncytial layer. There is no stroma nor bloodvessels, as the tumor is nourished by the blood in the vessels it invades.

**Spread.**—Spread is almost entirely by the blood stream, owing to the fundamental tendency of the trophoblastic cells to invade bloodvessels. Distant metastases in the lungs, etc., may be set up at an extraordinarily early date after an abortion. The secondary tumors are as hemorrhagic as the primary growth and show the same microscopic structure. Secondary nodules may appear in the vaginal wall. These are not implantations, for the tumor cells lie within vessels.

Not all cases run the rapidly fatal course of the ordinary chorionepithelioma. Some cases make a complete recovery when the primary growth is removed, and spontaneous disappearance of the metastatic growths has even been reported after this operation; this disappearance may be watched in the case of secondary nodules in the vagina. There is one small group of tumors (about 5 per cent) in which the structure is comparatively benign with a corresponding absence of bloodvessel invasion and formation of metastases. The growth consists of syncytial cells only, with no admixture of Langhans' cells. The tumor is therefore known as a *syncytioma*.

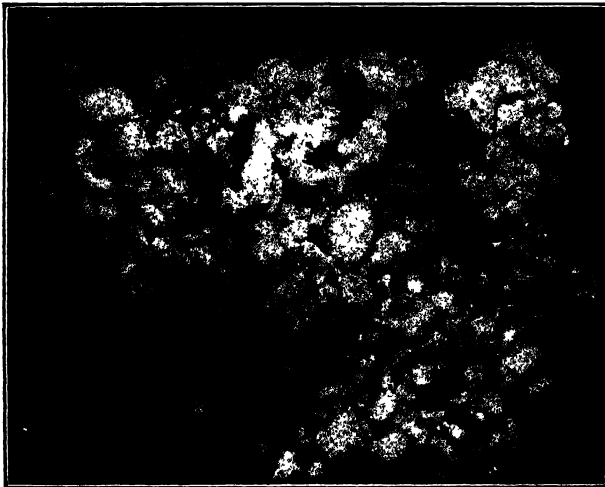


FIG. 345.—Hydatidiform mole.

### **PATHOLOGY OF THE PLACENTA**

**Hydatidiform Mole.**—The word mole means mass. A hydatidiform mole is a not uncommon condition (1 in 2500 or 3000 cases) in which the placenta is converted into a mass of grape-like bodies resembling hydatid cysts. (Fig. 345.) The cysts, which may be as small as a pin's head or as large as a grape, represent a cystic degeneration of the

connective tissue of the chorionic villi, but the fundamental condition is a proliferation of the epithelium of the villus, both Langhans' cells

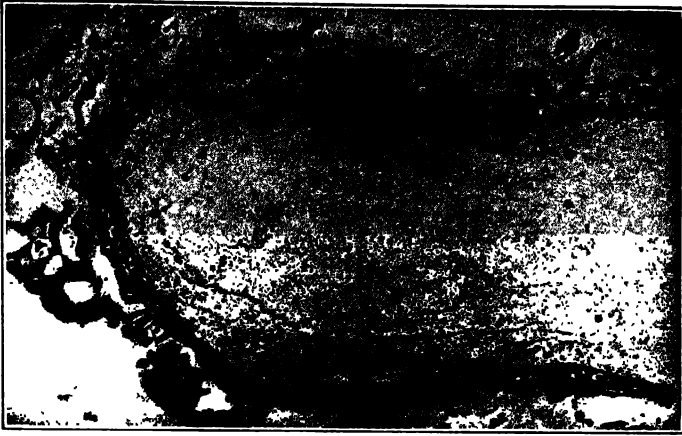


FIG. 346.—Hydatidiform degeneration of a chorionic villus. There is mucoid degeneration of the connective tissue and proliferation of the epithelium covering the villus.  $\times 25$ .

and syncytium, so that there are several layers of the former and the syncytial cells are unduly prominent. It may therefore be regarded as an innocent epithelial tumor, of which the malignant variety is the chorionepithelioma. When the change occurs early the fetus and placenta disappear, being replaced by a mass or mole composed of cyst-like bodies. When the change takes place later there may be a small atrophic fetus and remnants of placenta. Sometimes the change may be microscopic; these cases are much commoner than the fully developed ones. (Fig. 346.) The formation of a mole leads to abortion and may cause severe hemorrhage. We have already seen that at least part of the hormone which appears in the urine during pregnancy and gives the Aschheim-Zondek test for that con-



FIG. 347.—Placenta at full term. Above are vascularized villi with syncytial cells; below is decidua.  $\times 225$ .

dition is produced by the placenta. With the termination of pregnancy and complete removal of the placenta the test at once becomes negative. If portions of the placenta are retained or if hydatidiform mole or chorionepithelioma develop, the hormone continues to be produced and the test remains positive. When an innocent mole is removed the test becomes negative. If it remains positive it indicates that chorionepithelioma has developed. As long as active chorionic epithelium remains in the uterus, the test remains positive.

**Retained Placenta.**—After an abortion or a full-term pregnancy portions of placenta may be retained in the uterus. The villi may remain alive for many months and may appear perfectly normal when removed by the curette. The pathologist must therefore be cautious about expressing an opinion as to how long a time may have elapsed after the last pregnancy, especially in medico-legal cases. In the course of time the villi undergo hyaline degeneration. The stage to which pregnancy has advanced may be roughly estimated by remembering that before mid-term the villi are relatively avascular and the Langhan's cells are prominent, while after that time the villi become vascular and are covered only by syncytial cells, the Langhans' cells disappearing. (Fig. 347.)



FIG. 348.—Syphilitic placenta showing thickened and relatively avascular villi.  $\times 175$ .

**Utero-placental Apoplexy.**—This is a complication (possibly a cause) of premature separation of the normally implanted placenta. There may be most extensive hemorrhagic infiltration of the decidua and the uterine wall; (for an excellent colored plate see Williams' book). In one case which I examined the muscle fibers in places seemed to be floating in pools of blood. In this case the decidual vessels showed acute inflammatory changes which may have been the primary cause both of the uterine apoplexy and the separation of the placenta.

**Placental Infarcts.**—These are localized areas in the placenta, which may be red when they consist chiefly of coagulated blood, or pale yellow when the blood is decolorized and there is much necrosis of tissue. They constitute one of the commonest abnormalities of the placenta. Minute infarcts are indeed present in every placenta. Sometimes large wedge-shaped segments are involved. The accepted basis for the condition is an endarteritis of the vessels in the chorionic villi causing necrosis of the villi followed by coagulation of the blood between the villi, and matting together of the latter by fibrin. In many cases, however, no endarteritis can be found, so that another explanation must be sought. After the seventh month the Langhans' cells disappear and the syncytium may also atrophy in patches, as a result of which fibrin becomes deposited on the rough surface. The layer of fibrin cuts off the villi from their blood supply in the maternal sinuses so that they undergo necrosis. In this case the process is an ischemic necrosis but not an infarction. *Calcification* is not uncommon in these necrotic areas.

**Syphilis.**—When the fetus is syphilitic the placenta may be normal, but often it is thick and pale. The pallor is due to avascularity. The normal villi are very vascular, but in syphilis they may become markedly avascular owing to endarteritis, and considerably thickened. (Fig. 348.) In judging of avascularity it must be borne in mind that it is only in the second half of pregnancy that the villi are vascular, for in the earlier months they contain very few vessels.

**Tuberculosis.**—Tuberculosis is rare. Miliary tubercles may occur, or larger caseous masses.

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## THE FALLOPIAN TUBES

Although the only function of the Fallopian tubes is to carry the ovum from the ovary to the uterus, the mucous membrane shares in the general cyclic changes of menstruation. There are two types of epithelial cells, ciliated and non-ciliated. In the premenstrual phase the ciliated cells become much lower, and the non-ciliated cells project between them, with bulbous herniation into the lumen of the tube. During menstruation both sets of cells become low. This lowness is greatly accentuated during pregnancy, when they become almost flat. After menstruation the cells regain their normal height in three or four days.

The Fallopian tubes are peculiarly liable to inflammation. Tumors and other lesions are of little importance. The tubes may be infected from either end as well as from the blood stream. The narrow uterine opening, which is so easily closed by swelling of the wall, and the very numerous folds of mucous membrane tend to make an infection of long duration. Salpingitis or inflammation of the tubes is due to infection with the gonococcus in about 80 per cent of cases. Pyogenic cocci, especially streptococci, are responsible in about 15 per cent, and the tubercle bacillus in the remaining 5 per cent. Streptococci can be grown from the tubes many months or years after the primary infection, but the gonococcus may die out in the course of a few months.

## GONORRHEA

Before describing gonorrheal salpingitis it is convenient to make a brief survey of gonorrheal infection of the female genital tract. The primary infection is usually in the urethra, occasionally in the cervical

mucosa. Both of these are lined by a layer of epithelium which is readily penetrated by the gonococcus. The cornified squamous epithelium of the vulva and vagina is seldom infected except in children, in which it is soft and delicate. It is evident that when smears are made they must *not* be taken from the vagina, but from the cervix and urethra. The infection in the urethra usually gives rise to little or no clinical disturbance, so that it is difficult to determine with accuracy the date of infection. *Bartholin's glands*, situated on either side of the posterior commissure of the vaginal entrance, may become infected from the urethra, with the formation of an acute abscess. Acute Bartholinitis is almost always gonococcal in nature. The *cervix* is involved primarily or secondarily in most cases of gonorrhea, but as it is a very insensitive organ there are often no symptoms. It is in the mucous membrane of the cervical canal that the infection becomes chronic, for the branching racemose glands of the endocervix form an ideal lurking place for the gonococcus, from which it may issue periodically to infect other parts of the genital tract. Laceration after childbirth and gonorrhea account for nearly all cases of endocervicitis and cervicitis. The *endometrium of the body* of the uterus is seldom seriously infected. When first invaded by the gonococcus there are no doubt suppurative lesions of the superficial layers, but these are swept away at the next menstrual period, and it is seldom that chronic infection of a serious nature occurs. When the gonococcus reaches the *tubes* it finds as favorable a habitat as the endocervix, and the most serious results of gonorrhea in the female occur in the tubes. Before considering gonococcal salpingitis a few words may be devoted to gonorrhea in children.

*Gonorrheal vulvovaginitis* is practically confined to children, because in them the vaginal epithelium is not yet cornified and is readily penetrated by the gonococcus. The disease is extraordinarily contagious, and may sweep like a fire through a school or a children's hospital. The infection is spread by towels, sponges, etc., but often it is difficult to determine the exact means of spread. Once the infection is established it is very resistant to treatment. Anyone who has had practical experience with this disease in a hospital will be struck by the marked discrepancy between the laboratory findings and the clinical evidence of the disease. When routine vaginal smears are made in a hospital, Gram-negative intracellular diplococci are not infrequently found in children who show no symptoms of any kind. It is possible that in many cases the organisms seen are not gonococci but *Micrococcus catarrhalis*, which is morphologically indistinguishable from the gonococcus and is known to be capable of causing vaginitis in children. The distinction can readily be made by culture.

**Gonorrheal Salpingitis.**—Infection of the tubes may occur early in the disease, but there is often a considerable interval. During this time the gonococcus is lurking in the racemose glands of the cervix, from which retreat it may invade the tubes at any time. The infection is practically always bilateral. The effect depends entirely on the intensity of the inflammation. In mild cases it has the character of a catarrh, while in more severe form it becomes purulent. There is a tendency for both ends of the tubes to become closed even though the

inflammation be mild. The outer end may be closed by the inflamed fimbriæ becoming withdrawn into the ostium of the tube and adhering together, or by becoming adherent to the ovary. The inner end, which normally is less than 1 mm. in diameter, is easily closed by inflammatory swelling of the mucosa. The tube is now a closed cavity, and if a fluid exudate is poured out as the result of inflammation the tube will be distended. The distention is most marked at the distal end, and the tube becomes curved into a form like a retort. When the exudate is more or less serous (catarrhal salpingitis) the result is hydrosalpinx, when it is purulent a pyosalpinx is formed.

In *hydrosalpinx* the distention of the tube may be great, but the wall is thin and translucent, for there is no pronounced inflammatory thickening. The mucosa is atrophic, and the contents clear and watery, though rich in albumin. In *pyosalpinx* the wall is much thickened and the distended tube is filled with thick pus. The wall is infiltrated with inflammatory cells, polymorphonuclears in the early stages and lymphocytes and plasma cells later. In the tube as in the cervix the plasma cell is the characteristic cell of chronic inflammation. It is seldom that the gonococcus can be found in the pus except in recent cases, but secondary infection with *Bacillus coli* is rather frequent. If the inner end of the tube is not closed, there is no distention and the condition is called a *pus tube*. In *tubo-ovarian abscess* the inflamed fimbriæ adhere to the ovary, and infection of the ruptured Graafian follicle is a natural result. The gonococci flourish in the hemorrhagic tissue of the corpus luteum, and an abscess is formed which distends the ovary and communicates with the pyosalpinx by a narrow opening. The tube and ovary together form one large retort-shaped bag of pus. Very dense pelvic adhesions around the tubes and ovaries are a common result. *Salpingitis isthmica nodosa* is a peculiar condition in which nodules are formed at the inner end (isthmus) of the tube. As the result of persistent inflammation areas of mucosa are included in the deeper layers and may become separated from the lumen so as to give an adenomatous appearance. The condition is nearly always gonorrheal in origin, but is occasionally found in tuberculous salpingitis. It causes closure of the tube. From what has been said it is easy to see the relation which gonorrhea bears to sterility and chronic invalidism in women.

### TUBERCULOSIS OF THE FALLOPIAN TUBES

Tuberculous salpingitis resembles gonorrheal salpingitis in some respects, but differs from it in others. The mode of infection is quite different, being nearly always hematogenous from some distant focus, rarely from the peritoneal cavity in abdominal tuberculosis, and never from the lower genital tract. It is almost always bilateral, like the gonorrheal form, and is accompanied by adhesions which are even firmer and may make removal of the tubes quite impossible.

The tubes are thickened, and there may be tubercles on the serous

surface. The ostium usually remains open, in contrast to what occurs in gonorrheal salpingitis. Occasionally it may be closed, so that a



FIG. 349.—Tuberculous salpingitis.  
× 125.

*tuberculous pyosalpinx* develops, which may be indistinguishable from the gonorrheal form. The contents are characteristically thick and in old cases may become putty-like. Caseation, tubercle formation, epithelioid cells, and giant cells in the mucosa and other layers form a characteristic microscopic picture (Fig. 349.)

Infection may spread from the tubes to the peritoneum. Persistently recurring tuberculous peritonitis in the female sometimes clears up only when the tubes are removed.

#### TUBAL PREGNANCY

The ovum takes nearly a week to pass along the Fallopian tube from the ovary to the uterus, and it is during its passage down the tube that it becomes fertilized. If the impregnated ovum is arrested in the tube it may develop there and form a tubal pregnancy. The arrest is usually due to chronic

salpingitis, as a result of which the folds of the tube are thickened and deep glandular pockets are formed in which the ovum is entrapped. This explains the rarity of the condition in nulliparae, and the fact that there is often a long interval of sterility between the last pregnancy and the occurrence of the tubal pregnancy. The ovum is usually arrested in the outer end of the tube, the ostium becoming closed by the end of the second month. When development takes place in the inner part of the tube the ostium remains open.

There may be slight decidual formation in the tube, but it is never marked. The normal uterine decidua offers a good deal of resistance to invasion by the chorionic villi, and as this resistance is absent in the tube the villi are able to penetrate deeply into its wall. The ovum may burrow into the muscle, becoming separated from the lumen by the mucosa and some of the muscular layer. It now lies in a cavity in the wall of the tube, a cavity bounded on both sides by muscle and completely separated from the lumen which may be much narrowed. (Fig. 350.) A well-marked decidua is formed in the empty uterus, and this is sometimes expelled as a decidual cast. The uterus becomes enlarged owing to muscular hypertrophy caused by hormonal stimu-



lation. Uterine scrapings show decidual cells but no chorionic villi, a dissociation only found in extra-uterine pregnancy.



FIG. 350.—Tubal pregnancy. A large cavity in the wall of the distended tube is occupied by (1) chorionic villi; (2) dark blood clot; and (3) the gestation sac, which is the crescentic structure to the right with the body cavity in its lowest part. The lumen of the tube is seen to the left.  $\times 7$ .

The pregnancy is usually terminated before or at the end of the second month, although in rare cases it may go on much longer or even to full term. *Tubal abortion* is the common method of termination. Hemorrhage occurs into the gestation sac, destroying the embryo, distending the tube with blood so that it forms a *hematosalpinx*, and converting the products of conception into a *tubal mole* (*mole, mass*). The mole consists of firm blood clot in which chorionic villi are found

under the microscope, but no fetal parts. Blood escapes through the ostium if it is still open, the mole becomes detached, and may be extruded by the muscular contractions of the tube into the abdominal cavity. In very rare cases a mole formed in the isthmus of the tube has escaped into the uterus. At the time of the abortion there is a flow of blood from the uterus. This really comes from the uterus, not from the tube, being due to breaking down and discharge of the decidua. *Tubal rupture* occurs in about 25 per cent of cases. The wall of the tube is perforated by the trophoblast of the chorionic villi, bleeding occurs into the abdominal cavity, and the patient may die of internal hemorrhage. In rare cases the fetus may be slowly extruded through the ostium without severe hemorrhage. It may then be converted into a *lithopedion*, a mummified mass in which calcium salts are deposited.

### TUBAL CYSTS

Small *subserous cysts* about the size of a pin's head are common and are readily mistaken for miliary tubercles. They are probably formed from the peritoneum as the result of mild inflammation. *Cysts of the hydatids of Morgagni* are also fairly common. The cyst is about the size of a pea, filled with clear fluid, and attached by a slender stalk to one of the fimbriæ of the tube.

### TUMORS OF THE FALLOPIAN TUBES

All tumors of the tubes are very rare, although chronic inflammation is so common. Carcinoma (adenocarcinoma) is the most frequent variety; it is often bilateral. Primary chorionepithelioma has been described.

## THE OVARIES

**Descriptive Outline.**—It is important to realize the gross appearance of the ovary in health, otherwise the surgeon may (and not infrequently does) remove a normal organ. Each ovary is an elongated flattened body, the surface of which presents bosses (follicles, corpora lutea) separated by fissures and scars. The length is 2.5 to 5 cm., the width 1.5 to 3 cm., and the thickness 0.5 to 1.5 cm. The weight is 5 to 7 grams. Most of the surface is covered by glistening peritoneal mesothelium, but this changes to a lusterless surface (germinal epithelium) along the *white line* which marks the hilum of the ovary, i. e., the site of attachment of the mesovarium. The cortical zone contains ripening Graafian follicles forming cysts of varying size, sometimes up to 1.5 cm. in diameter. Still larger, and often mistaken by the ignorant for a pathological lesion, is the corpus luteum. In some cases it may occupy one-third of the ovary. The center is filled with fresh blood, and the wall is of a characteristic bright yellow color and an equally characteristic wavy convoluted outline. After the menopause the ovaries are small, hard and fibrous, often deeply fissured and scarred.

The essential element of the ovary is the germinal epithelium which is continuous embryologically with the endometrium and the lining of the Fallopian tubes. At birth the germinal epithelium covers the surface of the organ, but during development all the Graafian follicles are derived from this tissue. The maturation of the follicles and the fate of the follicles which do not mature are considered in connection

with the subject of cysts of the ovary. The ovarian stroma is peculiar in that it is not fibrous but entirely cellular, the cells being for the most part fusiform, though many of them are round. This cellularity must not be mistaken for evidence of inflammation or tumor formation.

### INFLAMMATION OF THE OVARIES

Inflammation of the ovary is usually the result of infection of the ovary from the Fallopian tube in the course of puerperal sepsis or gonorrhea. It is occasionally infected from the blood stream in infectious fevers.

Acute diffuse inflammation (oöphoritis) is generally caused by puerperal sepsis. The ovary is covered by the tough fibrous tunica albuginea which lies under the germinal epithelium and forms a formidable barrier to invading microörganisms. In puerperal sepsis there is pelvic peritonitis, so that the ovary may be bathed in pus containing virulent streptococci which overcome the barrier of the tunica albuginea and may cause an acute inflammation. Both ovaries are enlarged, congested, and contain numerous small abscesses. In general septicemia acute oöphoritis is a rare complication due to blood infection. The inflammation which may accompany mumps is non-suppurative.

*Ovarian abscess* is usually due to invasion of the ruptured Graafian follicle by the gonococcus. This may be rendered easy by fusion of the fimbriae of the tube with the ovary. It sometimes occurs in puerperal sepsis. The wall of the abscess is at first formed by the yellow wall of the corpus luteum, but in time the abscess involves the entire ovary which becomes converted into a bag of pus. This may fuse and communicate with the tubal abscess so as to form a tubo-ovarian abscess.

### CYSTS OF THE OVARY

Some of the cysts of the ovary are in the nature of retention cysts. Others are true epithelial tumors which assume a cystic form, and these will be considered in connection with tumors of the ovary.

During the course of the menstrual cycle a number of follicles approach maturity, the germinal epithelium proliferating to form several layers of *granulosa cells*. These follicles may develop along one of two lines. (1) The ripe follicle at mid-term of the cycle approaches the surface, discharges the ovum, and becomes converted into the *corpus luteum*, the granulosa cells proliferating and acquiring a high lipoid content which gives the new structure its yellow or lutein color. The corpus luteum is an organ of internal secretion which acts on the endometrium and the other developing follicles, but after menstruation it undergoes rapid hyaline degeneration, and becomes changed into a structureless white mass, the *corpus albicans*. If pregnancy supervenes the corpus luteum does not degenerate, and continues to increase in size. (2) Under the influence of the lutein hormone the other maturing follicles undergo retrogression or *atresia*. It is from these atretic

follicles, which may be regarded as examples of arrested development and are still lined by granulosa cells, that the majority of retention cysts probably arise. The stromal cells in contact with the developing follicle are known as *theca cells*. During atresia they become enlarged, acquire a lipoid content, and assume an epithelioid character, being known as *theca-lutein cells*.

**Follicular Cysts.**—These very common lesions of the ovary are retention cysts of atretic follicles. The cysts are small, seldom more than 3 cm. in diameter, multiple, and sometimes are so numerous as to involve the entire ovary, producing some enlargement. The cyst is lined by epithelium which is cuboidal in the small cysts but flattened in the larger ones. There is generally an associated fibrosis of the ovary, hence the old name of sclerocystic disease of the ovary. One cyst may grow at the expense of the others which it absorbs, and may reach the size of a plum or even a tangerine orange, the remaining cysts disappearing. The contents are clear and watery, and there is no trace of an epithelial lining in these larger cysts. In the ovaries of infants and even in the new-born there may be large numbers of small follicular cysts. These must be due to some abnormal hormonal stimuli (maternal); possibly some similar mechanism may be responsible for follicular cysts in the adult.

**Lutein Cysts.**—These cysts may represent degeneration of the corpus luteum formed after ovulation, or they may be *theca-lutein cysts* formed from atretic follicles lined by luteinized cells. The distinction between the two types is often difficult. Hemorrhage is frequent into both varieties. The hemorrhage may be severe, extend into the interstitial tissue, and form a *hematoma*. This may rupture into the abdominal cavity causing severe internal hemorrhage with symptoms simulating ruptured tubal pregnancy or some other abdominal catastrophe. The hemorrhage may prove fatal unless the ovary is at once removed.

**Endometrial Cysts (Chocolate-colored Cysts).**—These are examples of endometriosis, *i. e.*, ectopic development of endometrium-like tissue. They are small, often multiple, and of a dark reddish-brown color (chocolate) due to the presence of old blood. They are situated on the surface of the ovary and may show evidence of previous perforation. The cysts represent endometrial glands into which menstrual hemorrhage has occurred. The condition is probably an example of metaplasia due to hormonal stimulation of a tissue which is related developmentally to the endometrium rather than a result of endometrial implants.

### TUMORS OF THE OVARY

Tumors of the ovary may be *cystic* or *solid*. The former are very much more common, and are known as cystadenomas. They are for the most part innocent, though they may become malignant; the solid epithelial tumors, on the other hand, are practically all malignant. The cystadenomas may be divided into two main groups,

the pseudomucinous and the serous. These differ not only in their contents, but also in structure and behavior. There is a rare third group of tumors associated as a rule with sexual endocrine dysfunction for which there is no very appropriate name, but which may be called the *special group*.

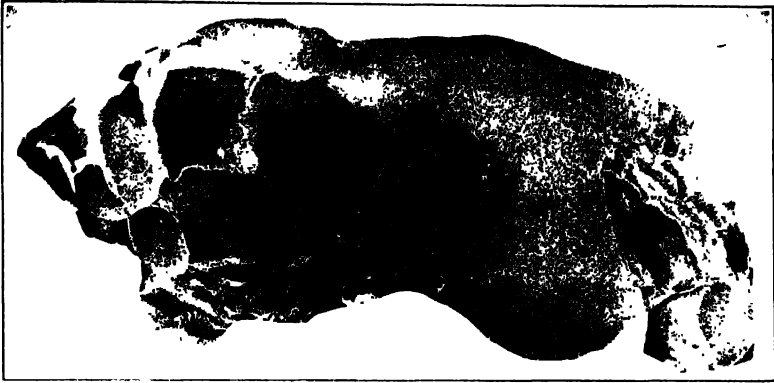


FIG. 351.—Pseudomucinous cystadenoma of the ovary. The cysts are filled with thick mucinous material which has been coagulated by the fixative.

**Pseudomucinous Cystadenoma.**—This is a common tumor, usually unilateral, and may reach very large dimensions. It is always multilocular, owing to the formation of daughter cysts from projecting buds of the lining epithelium. The daughter cysts vary greatly in size, a few may grow to a large size at the expense of the others, the inter-

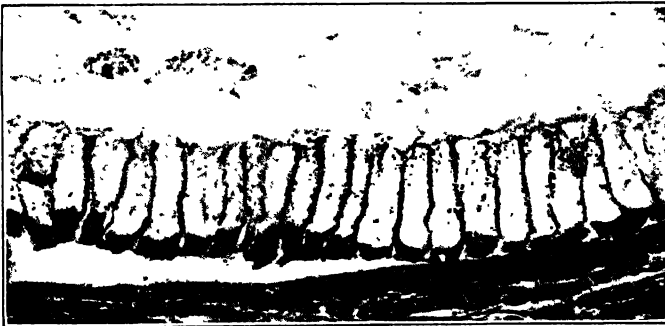


FIG. 352. —Pseudomucinous cystadenoma of the ovary. The palisade cells are filled with pseudomucin and the nuclei are displaced to the base.  $\times 500$ .

vening walls becoming broken down. The *contents* are very thick, mucoid, and stringy. (Fig. 351.) Though resembling mucin the material does not give the characteristic mucin reaction with acetic acid and is therefore known as pseudomucin. The fluid may be turbid and tinged with blood, or it may be shimmering with crystals

of cholesterol. The cyst develops a well-marked pedicle, and this may become twisted, producing intense congestion of the wall, hemorrhage into the cavities, and a clinical picture of acute strangulation.

The *microscopic picture* is characteristic. The cysts are lined by a layer of very tall columnar epithelial cells with extremely clear cytoplasm (due to the mucinous content) and nuclei situated at the base of the cells. (Fig. 352.) There may be small papillary projections from the wall of the cyst, but these are seldom pronounced. In the exceptional cases where there is marked papillary formation there is danger of malignancy; such cases are often bilateral. (Fig. 353.)

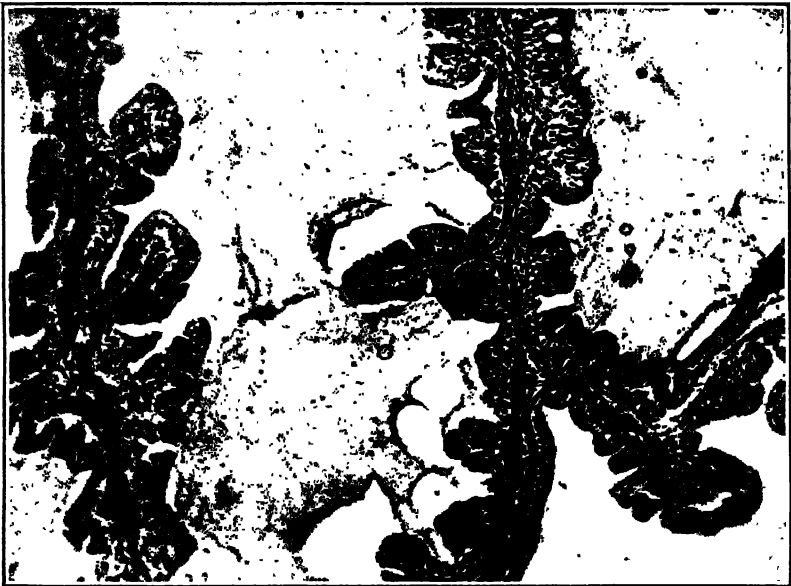


FIG. 353.—Pseudomucinous cystadenoma with papillary formation.  $\times 60$ .

There is the tendency to spontaneous perforation, but the pseudomucin seems to do little harm in the peritoneal cavity. In exceptional cases the tumor cells may become implanted on the peritoneum and produce large jelly-like masses, a condition known as *pseudomyxoma peritonei*. The prognosis is then bad, for the irritation of the new material sets up a chronic peritonitis, and repeated removal may fail to cure the patient.

**Serous Cystadenoma.**—This form, which constitutes about one-third of the cystic tumors of the ovary, may show different degrees of development. Thus there is the simple serous cyst which it may be difficult to distinguish from a large follicular cyst, the multiloculated serous cyst without papillary processes, and the multiloculated papillary serous cyst. The cystadenoma, which is frequently bilateral, resembles externally the pseudomucinous form, but it seldom has a

well-developed pedicle. The *contents* of the cysts are clear and watery; they contain no pseudomucin, but are highly albuminous. *Microscopically* the cysts are lined by an epithelium which is low compared with that of the pseudomucinous variety, nor are the cells filled with pseudomucin. They are said usually to be ciliated, but that has not been my own experience.

The most characteristic feature of these tumors is the presence of papillary processes, although these are not always present, so that the name papillary cystadenoma cannot be applied to the whole group. The presence of papillomata indicates a greater proliferative activity on the part of the epithelium, and the papillomata may appear on the outer as well as the inner surface, owing to invasion of the wall by the tumor cells. (Fig. 354.) This penetration does not prove that the condition has become malignant, but it is always suggestive. The



FIG. 354.—Serous cystadenoma of the ovary. The contents appear unusually thick, the albumin having been coagulated by the fixative. Papillary processes are present on the inner and outer surfaces.

papillary cystadenomas have a marked tendency toward malignant change, which is indicated by the soft character of the papillomata and the irregular arrangement of the epithelium. More or less of the original cyst structure may remain, with the malignant tissue represented by firm knobby areas, or the tumor, if highly cellular, may be soft and friable. In other cases the original cyst has been almost entirely replaced by tumor, so that the mode of origin may be more than doubtful. The malignant change may only be recognized microscopically. The percentage of these tumors which become malignant varies in different statistics from 20 to 65. The mere fact that carcinoma is found in such a tumor does not mean that the prognosis is necessarily bad, for the malignancy is not high, the growth is often circumscribed, and removal may be followed by complete cure. Secondary papillomata may be scattered over the peritoneum pro-

ducing an ascites which recurs repeatedly after tapping. The microscopic picture does not always correspond with the clinical course. There may be no microscopic evidence of malignancy, and yet the peritoneum may be covered with papillomata. On the other hand, cases of undoubted malignancy may run a very slow course and live as long as ten years. Calcification may sometimes occur; in one of my cases this involved a large area; it may even affect the glandular metastases.

The *origin* of the serous cystadenoma is undoubtedly the germinal epithelium either on the surface or in the form of down-growths into the ovary. The ciliated nature of the epithelium shows its relation to the epithelium of the rest of the genital tract. The origin of the pseudomucinous form is not so obvious, for the type of epithelium of which it is composed does not occur in the normal ovary. Those who have studied the matter most closely believe that the lesion represents a one-sided development of a teratoma in which the tall, columnar, intestinal type of epithelium has replaced the other elements of the growth.

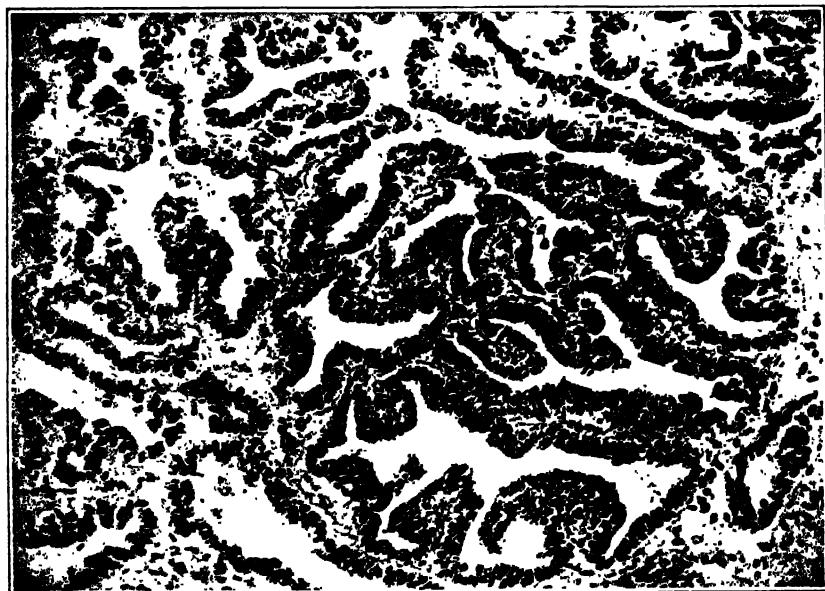


FIG. 355.—Papillary carcinoma of ovary.  $\times 100$ .

**Carcinoma.**—Carcinoma originating in the ovary is uncommon in comparison with metastatic carcinoma. The tumor is usually bilateral, one ovary being infected from the other. The tumor is of moderate size, and is usually soft and friable, though it may be firm if the stroma is abundant. The great majority of cancers of the ovary are malignant papillary cystadenomas, although the papillæ may coalesce so as to



give a solid appearance. (Fig. 355.) Thus a solid carcinoma may be a papillary cystadenoma which has become solid or it may be solid from the start. The latter may be of adenocarcinomatous or medullary type. The medullary form is usually composed of solid masses of carcinoma cells separated by a varying amount of stroma, but sometimes the cellular arrangement is diffuse and the structure highly anaplastic. Such tumors are easily mistaken for sarcoma, and their carcinomatous character is often not recognized.

Metastases are scattered over the surface of the peritoneum, and are responsible for the hemorrhagic ascites which is characteristic of the condition, and in a woman should always suggest the possibility of cancer of the ovary. There may be metastases in the uterus owing to infection by way of the Fallopian tube. In such cases it may be difficult or impossible to be certain if the cancer started in the endometrium or the ovary, for both are derived from a common type of epithelium.

**Secondary Carcinoma.**—These growths, which are nearly always bilateral, are of fairly frequent occurrence. The common primary sites are the stomach, large bowel, and uterus. The so-called *Krukenberg tumor* is characterized by large, round, vesicular cells with the nucleus pressed to one side by mucoid material so as to present a signet-ring appearance (Fig. 356), and separated by connective tissue showing mucoid degeneration. As a rule the primary tumor in the stomach or large bowel is a mucoid carcinoma, but this is not always the case. Apparently cancer cells growing in the ovary may acquire an ability to produce mucin which they do not possess in the primary lesion. The route of infection probably varies. In some cases it is no doubt due to implantation of cancer cells on the surface of the ovary. On the other hand the tumors are usually in the interior rather than on the surface of the ovaries. Retrograde lymph spread to the lumbar nodes and thence to the ovaries is a reasonable explanation in most cases. Blood spread is an occasional possibility.

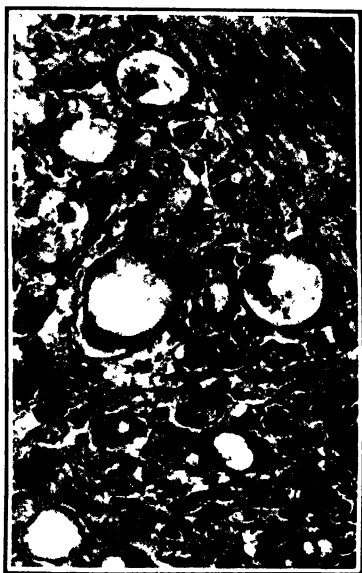


FIG. 356.—Krukenberg tumor showing signet-ring cells.  $\times 275$ .

### SPECIAL OVARIAN TUMORS

Of recent years a group of solid ovarian tumors have been described, some uncommon, others very rare, but all characterized by a probable common origin from embryonic remnants (cell rests) and in some instances marked by sex hormone disturbances. Three of these (granulosa-cell tumor, arrhenoblastoma

and dysgerminoma) have a common origin from the primitive mesenchyme of the ovary; the fourth (Brenner tumor) is unrelated.

In the developing ovary the granulosa layer of the follicles is formed by differentiation of the mesenchymal core of the gonad, not from the surface epithelium as used to be thought. The primitive granulosa cells are therefore connective tissue in type; only later do they develop an epithelial form. It follows that unripe tumors arising from these cells resemble connective tissue, whilst ripe tumors resemble epithelium; sometimes there may be a mixture of types.

The primitive gonad is neither ovary nor testicle, but may develop into either, the direction of development perhaps depending on the sex of the germ cells which invade the gonad from the primordial gut. Three errors of development are possible. (1) Embryonic rests of undifferentiated mesenchyme may remain and develop years later into a *granulosa-cell tumor*. Such a tumor will produce the female hormone with corresponding structural and functional disturbances. (2) In the primitive gonad male cells may be formed as a result of faulty development; these may remain as rests, and give rise in later life to an *arrhenoblastoma*, so-called because it produces a male hormone (*arrhen*, male) with corresponding functional disturbance. (3) Cells may be formed which do not develop along either a male or female line, and may be regarded as neuter. Years later these may give rise to tumors which naturally lack the power of producing hormones. In the ovary such a tumor is a *dysgerminoma*; in the testicle it is known as a seminoma. The *Brenner tumor* does not arise from the primitive mesenchyme of the ovary. Its origin is uncertain.

Much of the recent interest which has been aroused by these rare tumors is due to a series of papers by Robert Meyer. A summary of this work will be found in Novak's monograph.

**Granulosa-cell Tumor.**—This tumor is also called granulosa-cell carcinoma, but in less than 30 per cent of cases has evidence of malignancy developed. The size varies greatly from 1 or 2 cm. in diameter to a mass the size of an infant's head. Usually unilateral, the outline is sharply defined, the outer surface smooth, and the cut surface has a characteristic yellow tinge but is sometimes gray. It may present cysts of varying size, although the smaller tumors as a rule are solid.

The *microscopic appearance* is confusingly varied, and as different parts of the tumor may differ in structure, it is important to cut a number of blocks. Three main types may be distinguished: the follicular, diffuse, and cylindrical. In the *follicular type*, which is perhaps the most common, the granulosa cells are arranged in little clusters or rosettes around a central lumen. (Fig. 357, A.) To be distinguished from this lumen are the so-called Coll-Exner bodies, which are spaces in larger masses of granulosa cells produced by liquefaction. These spaces may contain bodies resembling and formerly mistaken for ova, but in reality they are secretion or degeneration products. In the *diffuse type* the granulosa cells are arranged diffusely rather than in rosettes. In the *cylindroid* or *cylindromatous* form masses of epithelial cells are separated by invasion and overgrowth of connective-tissue elements so that the appearance is one of anastomosing cylinders. Luteinization may occur, i. e., an accumulation of lipid in the tumor cells. This is readily demonstrated by fat stains. The more marked is this process, the more striking is the yellow color of the tumor. When the process is widespread the tumor is spoken of as a luteoma.

The *malignancy* is variable. Most cases pursue a benign course, the tumor often being found incidentally. In other cases there may be peritoneal recurrence a few months after removal of the tumor. The microscopic picture is of no value in determining the degree of malignancy.

Occasional tumors of this series present a connective-tissue appearance and are known as *theca-cell tumor*. The tumor, which is hard and fibrous, consists of interlacing bands of spindle cells rich in doubly refractive lipid and therefore giving the tumor a yellow color.

The *genesis* of these tumors is usually considered to be granulosa-cell rests which have not been used in the process of follicle formation. When one considers the intimate relationship which exists between the granulosa-cell and

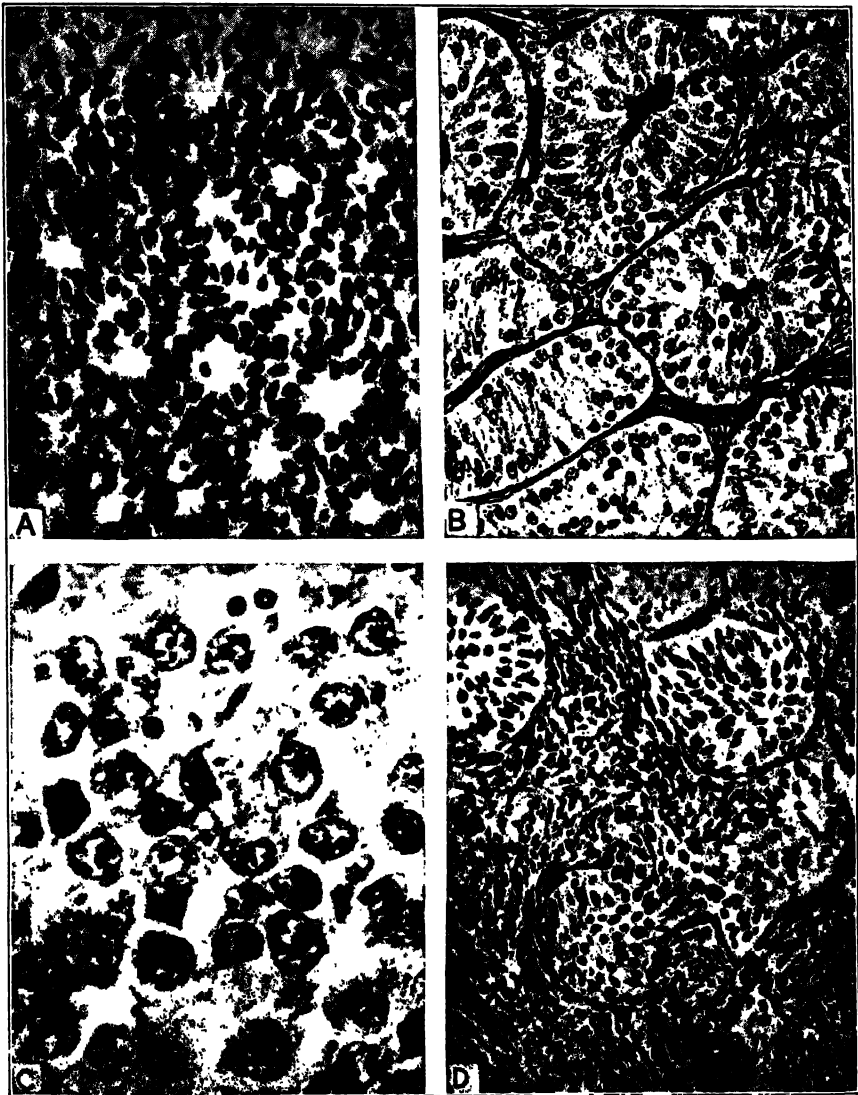


FIG. 357.—Special ovarian tumors: *A*, granulosa-cell tumor.  $\times 240$ ; *B*, arrhenoblastoma.  $\times 240$ ; *C*, dysgerminoma.  $\times 510$ ; *D*, Brenner tumor.  $\times 200$ .

theca-cell tumors, it seems more probable that their origin may be traced to primitive mesenchyme which antedates the differentiation of granulosa and theca cells.

The *clinical effects* of what has been called the feminizing tumor depend on the period of life at which the tumor develops. The granulosa cells produce estrogenic hormone, so that there will be abnormal menstrual bleeding before puberty or after the menopause, but during the reproductive years the only effect is likely to be increase in the flow. In the child there will be precocious puberty, *i. e.*, early menstruation, development of the breasts and external genitalia, and hypertrophy of the uterus. In the adult endometrial hyperplasia may be a marked feature. Carcinoma of the endometrium has developed in a number of cases, a point of interest in connection with the relation of sex hormones to carcinogenesis. Removal of the tumor in the prepuberty and postmenopausal cases is followed by disappearance of the abnormal clinical features.

**Arrhenoblastoma.**—This masculinizing tumor is the rarest member of the special ovarian tumors. It arises from the cells of the primitive ovarian



FIG. 358 —Arrhenoblastoma showing step-ladder arrangement of cells.  $\times 220$ .

mesenchyme which have a male tendency, and it is often found in the region of the rete ovarii, which is the homologue of the male testis. The *gross* appearance is similar to that of the granulosa-cell tumor. The *microscopic* picture varies even more widely than that of the latter tumor. In some cases, but these are the exception, there is perfect reproduction of the seminiferous tubules of the testis, a condition described long ago by Ludwig Pick as testicular adenoma of the ovary. (Fig. 357, B.) More usual is a very imperfect attempt at tubule formation, the cells being arranged for the most part in irregular columns. The nuclei often show a step-ladder arrangement which may suggest to the observer the true nature of the tumor. (Fig. 358.) At the far end of the scale the cells are completely undifferentiated, giving a picture of sarcoma. In such cases the pathologist is dependent on the characteristic clinical history. In spite of the sarcomatous appearance the tumor is either benign or of low malignancy.

The *clinical effects* are at first defeminizing, later masculinizing. Amenorrhea and extreme atrophy of the breasts are the early signs. These are followed later by hirsutism

with masculine distribution of hair, roughening and deepening of the voice, and hypertrophy of the clitoris. The picture is similar to that of tumor of the adrenal cortex, a structure with which the ovary is closely related developmentally.

**Dysgerminoma.**—This tumor, the name of which is also spelt disgerminoma, arises from indifferent cells of the mesenchyme in the gonad which fail to develop in either a male or female direction. It may occur in the ovary or testis. In the ovary it is often bilateral, may grow to a considerable size, and shows a characteristic yellow staining of the cut surface due to lipid degeneration.

*Microscopically* the tumor is simple in structure, and does not show the marked variation characteristic of the granulosa-cell tumor and arrhenoblastoma. The cells are large and round with vesicular nuclei (Fig. 357, C), but they shrink to a marked degree when embedded in paraffin, and are best seen in frozen or celloidin sections. They are grouped in solid alveoli or in

columns, separated by septa of fibrous tissue in which there may be large numbers of lymphocytes.

These tumors vary greatly in malignancy, nor does the microscopic picture help much in the prognosis, although the presence of numerous mitoses is of course a bad sign. The tumor is less malignant than the granulosa-cell tumor but more malignant than the arrhenoblastoma. In about 25 per cent of cases there are extrapelvic metastases.

The *clinical effects* are in striking contrast to those of granulosa-cell tumors and arrhenoblastoma, as might be expected from the fact that the tumor originates from indifferent sex cells. It usually arises in children and adolescents, but may occur in adults. As a rule the patient is normal sexually, but in a number of cases there has been pseudohermaphroditism, sexual hypoplasia or infantilism. This disturbance of development does not appear to be dependent on the presence of the tumor, because after surgical removal there has been no change in the clinical condition.

**Brenner Tumor.**—The lesion, described by Brenner in 1907 but clarified by Robert Meyer in 1932, differs sharply from the group of three "special" ovarian tumors already discussed. In the gross the tumor may take two forms, solid or cystic. The solid form, which is the usual type, tends to be small and resembles a fibroma, for which it is readily mistaken. When large, for reasons which soon will be apparent, it may take the form of pseudomucinous cystadenoma with nodular masses of tumor persisting in the wall. There are wide variations in size; it may be minute or it may be enormous.

The *microscopic picture* has none of the extreme variability so characteristic of granulosa-cell tumor and arrhenoblastoma. There are two essential elements: (1) nests of epithelial cells, and (2) fibromatous connective tissue separating these nests. (Fig. 357, *D*.) The epithelial cells are for the most part strikingly uniform in type, and recall the appearance of a carcinoid tumor of the appendix or bowel. There are no mitoses, nor any suggestion of malignancy. Cystic degeneration in the center of the nests is common, giving rise to an appearance which may be mistaken for follicles. One striking variation from the usual picture may occur, the cells becoming columnar and clear, secreting mucus, and lining spaces, a picture similar to that of a pseudomucinous cystadenoma. When this condition is widespread, the gross appearance may be identical with the ordinary cystadenoma, and the essential character of the original tumor may be overlooked. The connective-tissue elements vary, but may be so abundant that the lesion is mistaken for a fibroma.

The *origin* of the tumor is still a matter of dispute. The commonly accepted view is that of Meyer, who believes that the starting point is the so-called Walthard inclusions. These are minute circumscribed nests of cells which are found in the new-born and young child. Occasionally these take the form of gland-like spaces lined by columnar epithelium which may secrete mucus. Other suggestions are a dislocation of cells from the primitive urogenital tract, and one-sided development of a teratoma, the latter based on the frequent association with pseudomucinous cystadenoma.

The tumor is rare, but many cases must be overlooked. It is benign, of slow growth, and the majority are detected over the age of fifty. There is no endocrine disturbance.

**Dermoid Cyst.**—This is a teratoma, and is one of the common tumors of the ovary. In about 10 per cent of cases it is bilateral. It is of slow growth, and is almost invariably innocent, but in rare cases one of the elements of which it is composed may undergo malignant change. Its appearance is very characteristic, for it is of a yellow color and of a doughy consistence when removed from the body, although at body temperature the contents are fluid. The *contents*

consist of a yellow, greasy, buttery material containing a considerable amount of hair. The wall, which is lined by cubical epithelium, gives rise at one place to a nipple-shaped process covered by stratified epithelium and known as the *dermoid process*. This is the real tumor, for the other solid elements are derived from it. The commonest of these are skin and hair (hence the name dermoid), but bone, teeth, cartilage, brain, intestine, striated muscle, thyroid, adrenal, etc., may occur. In exceptional cases the thyroid tissue may proliferate to such a degree that the tumor consists almost entirely of this tissue. Such a condition is known as *struma ovarii*. It will be seen that the tumor contains constituents derived from all three germinal layers, and is therefore a true teratoma. The oily material which distends the cyst is produced by the numerous sebaceous glands with which the skin of the dermoid process is studded. (Fig. 359.) A dermoid begins as a solid tumor, and the cyst formation is secondary.



FIG. 359.—Dermoid cyst showing stratified epithelium and sebaceous glands.  $\times 60$ .

The dermoid cyst and the solid ovarian teratoma are commonly supposed to arise from one of the original blastomeres formed by the primary segmentation of the ovum, which has become separated and included in the ovary. It appears equally or even more probable that the tumor arises from one of the sex cells (ova) of the ovary.

**Solid Ovarian Teratomas.**—Solid ovarian teratomas are very rare tumors. They contain no fully formed structures such as skin and bone, but a variety of tissues usually in a rudimentary state, although well formed thyroid and other structures are sometimes present. They form soft solid masses which are highly malignant.

**Fibroma.**—Fibroma of the ovary is rare. Many of the lesions which used to be regarded as fibroma are now known to be examples of Brenner's tumor. It is a small, hard, white circumscribed tumor, and may arise in some cases from a corpus albicans.

**Sarcoma.**—Sarcoma is very rare.

Most of the tumors taken for sarcoma are probably anaplastic carcinomas. True sarcomas may occur as bilateral tumors in children, and present the usual soft homogeneous appearance. They are composed of round undifferentiated cells.

**Meigs' Syndrome.**—This term denotes a strange association of ascites, hydrothorax (usually right-sided), and a tumor of the ovary, usually but by no means invariably fibroma. Ascites is said to develop in association with 40 to 70 per cent of ovarian fibromas. Many theories have been suggested to explain the ascites and the less common hydrothorax. Rubin and his associates, recalling an old observation of Geibel's that an ovarian fibroma weighing 3200 grams lost 1150 grams of water in twenty-four hours, adduce

evidence in support of the view that the fluid comes from the numerous and large lymphatics at the hilum of the ovary. As ovarian tumors are covered by a single layer of low highly permeable epithelium, the fluid may readily escape. Transfer from the abdominal to the pleural cavity may be through the channels which connect the lymphatic networks on both sides of the diaphragm.

**Hypernephroid Tumors.**—One of the rarest of ovarian tumors is yellow in color and presents a picture of carcinoma composed of clear cells like those of hypernephroma. They are therefore called hypernephroid tumors, and are supposed to arise from mesonephric structures within the ovary (Saphir and Lackner).

### PAROVARIAN CYSTS

The parovarium, which represents a remnant of the sexual part of the Wolffian body, is situated in the mesosalpinx between the ovary and the Fallopian tube. It consists of a horizontal tube, the duct of Gärtner, homologous with the vas deferens, and a series of vertical tubes homologous to the vasa efferentia and epididymis. A parovarian cyst is situated between the layers of the broad ligament and may attain a great size. The wall is thick and lined by low, columnar, ciliated epithelium. Sometimes it shows warty papillary processes, but usually it is quite smooth. As the cyst occupies the broad ligament it may be mistaken for a serous cystadenoma of the ovary growing in that position. The intact ovary is attached to the side of the cyst, and the tube is stretched over the cyst and is greatly elongated. The condition is always innocent.

The so-called hydatid of Morgagni is a minute pedunculated cyst attached to the fimbriated end of the Fallopian tube. It is present in some 8 per cent of adults and is of no clinical importance. It appears to arise from the outer part of the epoöphoron (parovarium).

### THE VAGINA AND VULVA

**Soft Chancre.** Soft sore is an acute inflammatory venereal lesion which takes the form of multiple small ulcers over the external genitalia. They are shallow and have none of the induration so characteristic of syphilitic lesions. There is a marked tendency to the formation of suppurating buboes in the groin.

**Syphilis.**—A syphilitic lesion of the vulva may be primary or secondary. The primary lesion presents the usual appearance of a hard chancre, except that not infrequently there are lesions on both labia minora due to contact infection. The secondary lesions are mucous patches and condylomata.

**Condyloma Acuminata.**—This is a warty or papillary lesion, called "acuminata" because of its pointed form compared with the broad condylomata of syphilis. These warts, which cover the labia, are venereal in origin, being almost always due to gonorrhea. Microscopically there is hypertrophy of the connective-tissue papillæ of the skin, which grow outward, producing a warty appearance. The epithelium covering these processes is also thickened.

**Trichomonas Vaginalis Infection.**—Vaginal infection with *Trichomonas vaginalis* is being reported with increasing frequency. It is especially common in pregnant women, but is not confined to that state. The parasite is a pear-shaped flagellate measuring 7 to 30 microns in length, seen with great ease and vividness in the dark field. For this purpose the discharge is collected in a capillary pipette, which is placed in a test-tube and sent at once to the laboratory. The patient may have an acute inflammation of the vagina, with a profuse seropurulent discharge which is often foamy or bubbling, and

contains large numbers of bacteria and flagellates. There is still difference of opinion regarding the pathogenicity of the parasite.

**Leukoplakia and Kraurosis.**—*Leukoplakia* of the vulva may occur in the later years of life and is usually associated with intense pruritus. There is marked thickening of the epidermis, this thickening including both the stratum corneum and stratum Malpighi. The great clinical importance of the condition is that it is often precancerous, and may develop into epidermoid carcinoma. *Kraurosis vulvæ* (*krauros*, dry) is a closely related condition characterized by marked shrinkage of the external genitalia which become dead white and wrinkled like parchment. The stratum corneum is thick, but the stratum Malpighi is very thin and atrophic, the papillæ disappear, and the epidermis takes the form of a narrow straight band. Chronic inflammatory cells are present in the underlying tissue. The lesion is often associated with leukoplakia, and may be regarded as a variety of that condition. Occasionally it is precancerous.

**Tumors.**—*Carcinoma of the vulva* is not uncommon. It is nearly always preceded by some precancerous condition such as leukoplakia, kraurosis, gonorrheal warts, or other evidence of chronic inflammation. It is epidermoid in type, and early metastases occur in the inguinal lymph nodes. *Carcinoma of the vagina* is less common; it presents the same characteristics. *Mixed tumor of the vagina*, so-called sarcoma of the vagina, is the same tumor as the "grape-like sarcoma" of the cervix. It is a malignant tumor of children, and is composed of mucoid tissue, plain and striated muscle, etc. Owing to mucoid degeneration many cyst-like structures may be formed.

**Urethral Caruncle.**—This not uncommon condition takes the form of a small, bright red, exquisitely tender, polypoidal mass which arises from the opening of the urethra and projects into the vestibule. Its structure varies, but it may be regarded as a capillary angioma, consisting of telangiectatic or highly vascular connective tissue infiltrated with round cells and covered by squamous epithelium.

## CONGENITAL ANOMALIES OF THE FEMALE GENITAL TRACT

A great variety of defects may occur in the course of the development of the female genital tract. Only the more common ones can be referred to here. For further details works on gynecology must be consulted.

**Uterus.**—The uterus and vagina are formed by fusion of the lower part of the Müllerian ducts, the upper parts remaining separate to become Fallopian tubes. This *fusion may be incomplete*, so that there may be a double uterus and vagina, a single vagina and double uterus, or the uterus may only be divided in its upper part so that it seems to have two horns (*uterus bicornis*). Splitting of the upper part of the Müllerian ducts gives rise to two Fallopian tubes on each side. *Hypoplasia* (persistence after birth of the infantile type of uterus) is part of a general infantilism, such as occurs from thyroid or pituitary deficiency. *Absence* of the uterus is very rare. *Atresia* or closure of the os leads to an accumulation of menstrual blood in the uterus. If one of the Müllerian ducts does not develop, there will be absence of one of the tubes and the uterus is asymmetrical. Persistence of portions of the Wolffian ducts in the wall of the vagina may lead to the formation of cysts and tumors.

**Ovaries.**—Hypoplasia of the ovaries is associated with general hypoplasia of the genital system. The ovary may be displaced, *e. g.*, in a patent canal of Nuck. Displacement of the germinal epithelium may occur, and it is possible that the common cystadenomas of the ovary may arise from such displaced portions.

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## CHAPTER XXVII

### THE BREAST

**Pathological Physiology of the Breast.**—The previous chapter was opened with a discussion of menstruation, because without some understanding of that function and of the structural changes which occur in the uterus as the result of ovarian stimulation much of the pathology of the uterus must be incomprehensible. The same is true of the breast. For this is not a static organ, but one undergoing constant periodic change as the result of control from the ovaries, and if this control becomes abnormal or irregular the change will cross the border-line between the physiological and the pathological. It is a truism that pathology is merely disordered physiology, but in no field is it so important to realize this truth as in the pathology of the breast.

In the *newly-born*, both male and female, there may be mammary swelling and secretion due to the presence in the blood of the female sex hormone which can also be demonstrated in the urine. This soon passes off, and the breast remains dormant until puberty, when marked activity becomes apparent in girls owing to stimuli from the ovaries. Up to the time of puberty the parenchymatous tissue of the breast consists only of ducts. At *puberty* under the influence of ovulation and the formation of the corpus luteum active budding of the ducts occurs, and from these buds the acini are formed. The influence of the ovary is indicated by the following facts. (1) The breasts do not develop if the ovaries are infantile or absent. (2) Reimplantation of the ovaries in the castrated animal at once stimulates mammary growth. (3) Injection of corpus luteum extract will produce breast hypertrophy in an animal.

It is during *pregnancy* and *lactation* that the changes are most marked. The breast of a pregnant woman differs completely from that of a virgin, being composed of a mass of glandular tissue which entirely replaces the fat. The changes characteristic of pregnancy consist of two phases, the proliferative and the secretory. The phase of *proliferation* is due to the action of the corpus luteum of pregnancy and the placenta, and is characterized by rapid proliferation of epithelial buds from the ducts with formation of new acini, marked increase of the connective-tissue mantle of the lobules (see below), and infiltration of this tissue with round cells. When the placental stimulus is withdrawn as the result of delivery or abortion, proliferation ceases and the stage of *secretion* (lactation) begins. Placental activity is evidently antagonistic to the secretory function of the breast, for lactation ceases when a new pregnancy develops; possibly this is related to the development of a new corpus luteum. At the end of lactation there is a fresh invasion of lymphocytes. These must not be regarded as an evidence of inflammation, for their function is apparently the removal of cell debris and secretion. After lactation comes involution. The glandular overgrowth disappears to a great extent, but the breast does not return to its original state, for some epithelial and fibrous hypertrophy (lactation hypertrophy) always remains, and this incomplete involution may have an important pathological bearing in the shape of cystic dilatation of the ducts.

At the *menopause* the breast undergoes marked atrophy with disappearance of the glandular tissue. This atrophy is not continuous, but is often interrupted by irregular proliferation which in turn is dependent on the irregular cessation of ovulation as indicated by menstrual disturbance. Here again there may be cyst formation as the result of incomplete involution.

The normal virgin breast in the intermenstrual period (from the fifth to the fifteenth day) consists of a small number of ducts with associated rudimentary acini, duct and acini being surrounded by a specialized loose connective tissue quite distinct from the general stroma of the gland. This specialized tissue is called the pericanalicular and periacinar connective tissue, but may for convenience be spoken of as the periductal tissue. The combined glandular and connective tissue form a series of islands known as lobules or gland fields. (Fig. 360.) The periductal tissue must not be dissociated from the epithelial structures, for it shares with them the normal response to ovarian stimulation, and also plays an important part in pathological changes.

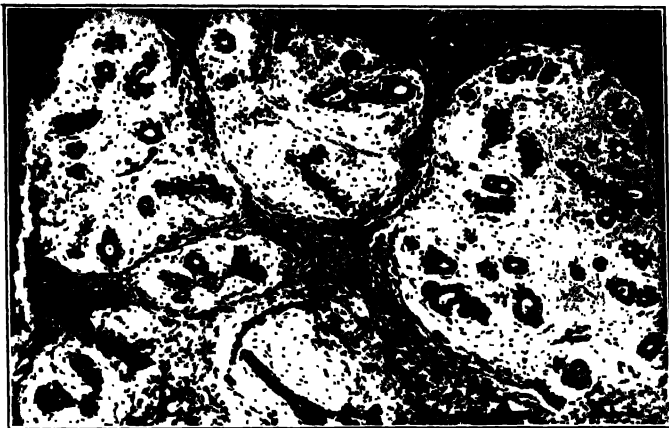


FIG. 360.—Gland fields of the breast. Six units are shown, each consisting of a group of ducts surrounded by specialized pale connective tissue. Changes in these units are the basis of cystic hyperplasia and fibroadenoma.  $\times 75$ .

It is probable that the breast undergoes changes analogous to those seen in the endometrium, although it is much more difficult to be certain of this than in the case of the uterus (Rosenburg). The epithelium of the ducts undergoes hyperplasia together with myxomatous change in the periductal tissue of the lobules and infiltration with lymphocytes, a condition which may be mistaken for so-called chronic mastitis. When the ovarian stimulus is withdrawn hyperplasia gives place to involution. The microscopic appearance so often seen in surgical material as the result of exuberance of these physiological processes is what Cheatele calls *mazoplasia*. The wide morphological variations which may occur are beautifully illustrated in Ingleby's paper.

The normal cycle may be interfered with. This interference usually takes the form of ovarian overactivity, and the result may be regarded as undue hyperplasia or delayed involution, which are merely two ways of looking at the same thing. Disturbances are most likely to occur at two periods of the reproductive life of the woman: (1) during the years of developing sexual activity, and (2) in the years preceding the menopause when ovarian function is becoming irregular. The stimulation of growth or the interference with involution may be local or general and may chiefly affect either the epithelium or the connective tissue of the gland fields, although both are usually involved to some degree. (1) Localized hyperplasia of the gland fields due to undue ovarian stimulation results in the *painful nodules* which may develop in the breasts of young women at the menstrual period. (2) Diffuse epithelial hyperplasia and lack of involution is seen in the preclimacteric years particularly in breasts that have undergone repeated lactation, and is usually

associated with cyst formation. This is the condition commonly known as *chronic mastitis*, but which would be better named lobular hyperplasia or cystic hyperplasia. (3) Localized epithelial hyperplasia which occurs in a distended duct results in the formation of a *duct papilloma*. (4) Localized hyperplasia most marked in the connective tissue of the gland fields will give rise to *fibroadenoma* which may be encapsulated or non-encapsulated. The ducts may be invaginated by the proliferating fibrous tissue, giving rise to the *intra-canalicular* form of fibroadenoma. It is natural that these changes should not infrequently be combined in the same breast. (Fig. 361.)



FIG. 361.—Section of breast showing a combination of cystic hyperplasia and fibroadenoma.  $\times 40$ .

### LOBULAR HYPERPLASIA (CHRONIC MASTITIS)

Lobular hyperplasia of the breast is the analogue of endometrial hyperplasia in the uterus. Both are manifestations of aberrant physiology in an organ which is the scene of constant epithelial unrest, and are therefore extremely common. In the breast the condition is commonly known as chronic mastitis, and is the commonest of all mammary lesions. Its names are legion and indicate the uncertainty which has existed as to its nature; among the commoner are chronic mastitis, chronic cystic mastitis, chronic interstitial mastitis, diffuse fibroadenoma, cystadenoma papilliferum, involution cysts, abnormal involution, cystic disease of the breast, Schimmelbusch's disease. To the writer it appears that the best name is lobular hyperplasia, suggested by R. P. Smith. This takes cognizance of the lobules or gland fields which constitute the basic unit of breast architecture. Smith's paper consists of only three paragraphs, the last of which may be

quoted in full. "The new terminology proposed is, therefore: lobular hyperplasia—localized or generalized, cystic or non-cystic. Such a classification embraces the majority of the older names. For example, generalized non-cystic lobular hyperplasia corresponds to mazoplasia (Cheatele), the mastopathia of Whitehouse, and the painful nodular breasts of young women, so well known clinically; localized cystic lobular hyperplasia to the solitary blue-domed cyst of Bloodgood; generalized cystic lobular hyperplasia to cystic hyperplasia, involution cysts, abnormal involution cystic disease, and Schimmelbusch's disease, where multiple cysts are scattered throughout the breasts. As the sole cause for regarding the condition inflammatory is the presence of collections of lymphocytes, which are a normal feature in every pregnancy and lactation, and to a lesser degree at every menstrual period, the terms chronic mastitis, chronic cystic mastitis and chronic interstitial mastitis, can be dismissed as archaic and should be discarded." Unfortunately it is not easy to cast overboard a term which has become part of the everyday speech of pathologists and surgeons, and it would almost require the edict of a dictator to displace it from medical literature. As long as the term chronic mastitis is merely a symbol, albeit a meaningless one, its use can be tolerated. The probable cause is abnormal or excessive stimulation from the ovary. Marked mammary glandular hyperplasia can be produced in the mouse by daily injections of ovarian extract. Moreover it is found that estrin tends to cause albuminous secretion and cystic dilatation, while progesterin leads to epithelial hyperplasia. It is probable that lobular hyperplasia of the breast is due to the action of both ovarian hormones, the corpus luteum phase predominating.

**Clinical Features.**—The patient is usually in the involutionary period of life, at a time when the ovarian function is irregular and declining. Another group is seen in young unmarried women who often present evidence of disturbance of ovarian function. They really suffer from hypoactivity of the ovaries (short and scanty menstruation) with overactive or persistent corpora lutea. The condition is commoner in multiparæ, whose breasts have repeatedly passed through the periodic hyperplasia and involution of pregnancy and lactation. The woman complains either of pain or a lump in the breast; the pain is usually worse at the menstrual period. There is tenderness as well as pain. Both breasts are often involved, and there may be several lumps in each breast, which always suggests an innocent condition. The suspensory ligaments of the breast are often thickened after lactation, and as these are attached to the skin the effect is to isolate lobules of fat which appear to be separate nodules when the breast is palpated. After the breast is removed these nodules can no longer be felt owing to division of the suspensory ligaments. The breast may feel coarsely granular owing to the presence of small cysts; such cysts always feel as hard as a tumor, never soft and fluctuating. The axillary lymph nodes may be enlarged and tender for a reason which is not obvious.

**Lesions.**—The *gross appearance* is characteristic, and it is usually easy to make a naked-eye diagnosis when the specimen is removed.

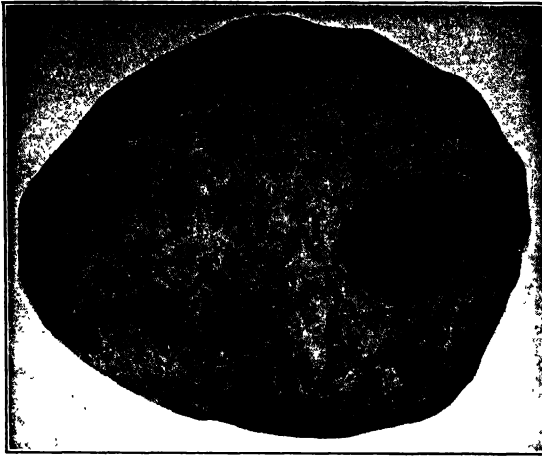


FIG. 362.—Lobular hyperplasia with cyst formation. All of the tissue shown is the seat of a diffuse induration. There are several cysts of varying size and many very minute cysts.

The lesion is *diffuse*, so that the indurated area is not circumscribed as is cancer, but shades off into the surrounding tissue. It is characteristically tough and india-rubbery in consistence, on that account dif-



FIG. 363.—Cysts in lobular hyperplasia. Both epithelial proliferation and cyst formation are present. There is commencing papillary formation in the large cyst.

ficult to cut in comparison with carcinoma, yellowish-white or gray in color, and not encapsulated. Cysts of varying size and number are usually present. (Fig. 362.) The dilated ducts may be filled with putty-like material which can be squeezed out like worm casts. The cysts are

commonly multiple and small. Sometimes there is a single large cyst tensely filled with fluid and commonly called the blue-domed cyst (Bloodgood). If there are many large cysts the picture becomes that of the classical cystic disease of the breast or Schimmelbusch's disease in which the breast may be riddled with large, smooth-walled cysts.

The *microscopic appearance* is extremely varied, depending on whether hyperplasia or involution dominates the process. If hyperplasia is the chief feature, the picture will be adenomatous in type, a condition described by some authors as non-encapsulated adenoma, and more likely to be seen in the earlier years. If involution is dominant, cyst formation will be a striking feature, and is therefore seen more often in the later years. As the hyperplasia may chiefly affect either the epithelium or the connective tissue of the gland fields, the picture will be correspondingly varied, some cases showing marked epithelial proliferation and papillary formation, while others show marked fibrous overgrowth and may resemble fibroadenoma.

The varied picture presents one or more of the following features. (1) *Glandular hyperplasia* is usually marked as evidenced by the number and prominence of the gland fields. This is the essence of lobular hyperplasia. The acini are represented by solid buds of cells which stain darkly. This appearance is likely to be found in younger women. (2) *Cyst formation* is so common that it has been incorporated in such names as cystic mastitis. (Fig. 363.) The cysts are usually small, they may be microscopic in size, or they may be as large as a cherry. The cysts are formed from the ducts, not as the result of obstruction by fibrous tissue nor distention by secretion, but because the hyperplastic duct has not undergone complete involution to the normal size. When a cyst is once formed, secretion may add to its size. (3) *Papillary formation* may be very striking owing to the epithelial cells growing in bud-like formation into the cyst spaces. Trabeculae of cells may spread across the smaller cysts, coalescing in places so as to form an interlacing filigree or laciform pattern, which some writers describe as adenomatous. This intraductal epithelial proliferation may progress to such a degree that the entire lumen becomes packed with cells. It may be very difficult to distinguish this condition from carcinoma, and in some cases actual invasion of the surrounding tissue may occur. (4) *Pink epithelial cells* may line the cyst or form the papillary processes. (Fig. 364.) Part of a cyst may be lined by normal cells, and part by these large cells, the cytoplasm of which stains pink with eosin. The change appears to be due to hyalinization of the epithelium. The cytoplasm of these cells when suitably stained is found to be filled with granules, and the appearance of the cells is identified with that of the cells of the specialized apocrine sweat glands in the axilla and elsewhere (Lendrum). Both mammary epithelium and the epithelium of apocrine glands arise from primitive sweat gland epithelium, and it seems probable that the mammary epithelium may become dedifferentiated to the primitive sweat gland type, and in the subsequent regeneration acquire the characteristics of

apocrine sweat gland epithelium. (5) *Connective-tissue hyperplasia* is an integral part of the process, but varies greatly in amount. It is the specialized connective tissue of the gland fields which is involved, not the stroma of the breast. The overgrowth may be so great that the condition is practically one of pericanalicular fibroma. (6) *Lymphocytic infiltration* is a very common feature, and is responsible for the misconception that the condition is a mastitis. The round cells are not due to infection, for they are present in the hyperplasia of pregnancy, lactation and menstruation, where they apparently have some scavenger action to perform.



FIG. 364.—Cystic hyperplasia with papillary formation. The papillary epithelium stained pink with eosin.  $\times 90$ .

The valuable contributions of Sir Lenthal Cheate to the subject of cystic hyperplasia must not pass unnoticed, although his nomenclature is so forbidding as to prevent adoption for every-day use. Briefly summarized, Cheate divides the disease commonly called chronic mastitis into two entirely different conditions. (1) *Mazoplasia*; this is characterized by hyperplasia of pericanalicular and periacinar connective tissue, round-cell infiltration, and the formation of new ducts and acini. It is very common, being almost universal in women who have borne children, less common in virgins, and is seen at birth, puberty, pregnancy, and lactation. There is no cyst formation, no relation to cancer, but it may cause fibroadenoma. (2) *Schimmelbusch's disease*; this is a special (cystophorous) type of what Cheate calls desquamative epithelial hyperplasia, characterized by the formation of cysts and papillary processes. It is the condition which we have called lobular hyperplasia. The hyperplasia may develop into neoplasia, sometimes benign but often malignant. Cheate regards the condition as strongly precancerous.



**Relation to Carcinoma.**—The question of the relation of lobular hyperplasia (chronic mastitis) to carcinoma is a very difficult one, regarding which there are great differences of opinion. The condition is commonly regarded as precancerous and a radical operation is often done lest a worse thing should befall the patient. This may be advisable in an elderly patient, but is certainly unjustifiable in a young woman. The writer feels that from the pathological point of view it is possible to trace a long series of progressive changes in the duct epithelium, until the ducts are filled with masses of cells which are indistinguishable histologically from cancer cells and which may finally break through the wall and invade the surrounding tissues. (Fig. 365.) Actively



FIG. 365.—Carcinoma of the breast associated with cystic hyperplasia. (From Boyd's Surgical Pathology.)

proliferating lesions such as intraduct papilloma and cysts with papillary epithelium are of graver import than large cysts with atrophic epithelium. Greene has observed a strain of rabbits many of whom developed cystic disease of the breast followed by carcinoma. The cystic disease phase was identical with Schimmelbusch's disease in women. Within the cysts there occurred first epithelial hyperplasia, then neoplasia, and finally invasion. These changes were watched by means of repeated biopsies. From the pathological standpoint, therefore, the condition must be regarded as precancerous. The final court of appeal should be follow-up studies on women who have had complete (but not radical) removal of the gross lesion. Unfortunately there is no unanimity on this point in the published reports. Blood-

good, and more recently Campbell, conclude from such studies that there is no causal relationship between the two conditions, although both are common lesions of the breast occurring mostly at the same age period. Shields Warren, on the other hand, as the result of similar studies, believes that a woman who has had chronic mastitis is in far greater danger of developing cancer, even though all the apparently abnormal tissue has been removed, but once she has passed the menopause there is no greater danger than in any control group. If a malignant change does occur it is apparently of a limited character, which differs markedly from the invasive character of an ordinary primary carcinoma in which early removal is often of no avail.

**Fibrosing Adenomatosis.**—Ewing has drawn attention to this condition which he says gives rise, probably more frequently than any other lesion of the breast, to a mistaken diagnosis of cancer. It is commoner in young women. The breast contains a number of hard discrete nodules, the cut surface of which is uniform in contrast with that of carcinoma. The microscopic appearance is described by the name, for there is multiplication of the acinar cells combined with fibrosis, the latter dominating the picture and finally leading to atrophy. There is a tendency for the acini to break up into small groups and clumps of cells. The picture is a characteristic one. The condition bears no relation to malignancy.

### FIBROEPITHELIAL TUMORS

When the hyperplasia which is characteristic of aberrant breast physiology is localized, a nodular condition is produced which is commonly regarded as a tumor. The hyperplastic area may be semi-encapsulated, being sharply demarcated on one side but continuous with the breast tissue on the other. The hypertrophy may be great enough to push the fibrous tissue aside so that a complete capsule is formed. If the overgrowth chiefly affects the connective tissue we speak of a *fibroma*. As a rule both epithelial and fibrous tissues share in the overgrowth, giving a *fibroadenoma*. Localized epithelial overgrowth into a dilated duct forms a *duct papilloma*.

**Fibroadenoma.**—A fibroadenoma occurs chiefly in young women, originating perhaps at puberty and growing during the years of developing sexual activity. It is commoner in nulliparæ than in those who have borne children, differing in this respect from lobular hyperplasia.

It is customary to recognize two forms of tumor, the intracanalicular and the pericanalicular. The *intracanalicular fibroadenoma* is the common variety. (Fig. 366.) As the hyperplasia involves particularly the specialized connective tissue of the lobules, the tumor is more a fibroma than an adenoma. It is usually well encapsulated, has a soft consistency and a rather moist appearance, and the cut surface may show many narrow slits or splits (the ducts), so that the appearance may resemble the leaves of a book; sometimes little masses can be distinguished enclosed within small spaces. The encapsulation may be only partial, the tumor blending on one side with the surrounding breast tissue. *Microscopically* there is a great proliferation of loose connective tissue of open structure which invaginates the wall of the

ducts, projecting into the lumen to form polypoid masses, and producing great dilatation, elongation, and distortion of the ducts. (Fig. 367.) The connection of these polypoid growths with the wall of the duct is often not seen in the section, so that fibrous masses covered by a layer of epithelium appear to be lying free in the lumen. The ordinary connective stroma of the breast takes no part in the overgrowth. The lobules of the surrounding tissue often show hyperplasia, and in those cases where the encapsulation is only partial the similarity of structure of the tumor and the adjacent tissue may be very striking.



FIG. 366

FIG. 366.—Intracanalicular fibroadenoma. The process of formation is shown here, but usually no connection can be seen between the mass within the duct and the surrounding wall.  $\times 175$ .



FIG. 367

FIG. 367.—Intracanalicular fibroadenoma of the breast. The ducts are elongated and distorted by the new fibrous tissue.  $\times 75$ .

The *pericanalicular fibroadenoma* is a much harder tumor, and seldom becomes as large as the preceding variety. It is well encapsulated, and when the sheath is incised it can usually be shelled out quite readily. It has a characteristic mobility when palpated. The cut surface is white, dry, and homogeneous. *Microscopically* there is a proliferation of glandular and fibrous tissue. The new connective tissue surrounds the ducts without invaginating them, hence the name *pericanalicular*. (Fig. 368.) The picture suggests less active growth than that of the preceding variety.

The distinction between the two forms, however, is not fundamental.

Examine the intracanalicular type and many areas of pericanalicular formation will be found. Taking the broader view we may say that a fibroadenoma may be predominantly intracanalicular or pericanalicular in type. The recognition of the two forms is customary but somewhat unnecessary.



FIG. 368.—Pericanalicular fibroadenoma. The ducts are surrounded by the new fibrous tissue.  $\times 200$ .



FIG. 369.—Duct papilloma of the breast. The duct is greatly distended by a raspberry-like mass.  $\times 10$ .

**Duct Papilloma.**—This condition is also known as adenocystoma, papillary cystoma, intracystic papilloma, and many other names. The papilloma projects into a dilated duct, usually in the vicinity of the nipple. At first it is composed of a series of folds so that it resembles a small raspberry, but as it increases in size the folds or villi adhere together so that the surface becomes smoother. Finally it distends the duct and becomes a solid compact mass. *Microscopically* the tumor consists at first of numerous delicate villi covered by epithelium, but as it increases in size and the processes are pressed together, adhere and interlace, gland-like spaces are formed so that the appearance becomes adenomatous. (Fig. 369.) This explains the use of such a term as adenocystoma. The bloodvessels are numerous and thin-walled so that hemorrhage is common, and a blood-stained discharge from the nipple is one of the characteristic symptoms. In some cases a malignant change develops and the condition becomes a duct carcinoma.

**CARCINOMA OF THE BREAST**

Cancer of the female breast is one of the commonest forms of malignant disease. It usually occurs during the involution period, *i. e.*, in the years before the menopause, and is rare before the age of thirty-five years. There is a higher incidence in nulliparæ, and the disease bears no relation to repeated suckling. Pregnancy indeed appears to have a protective influence.

**Etiology.**—Three factors which are of importance in the experimental animal and perhaps also in the human subject are inadequate drainage of the duct system with stagnation and retention of irritating material (Adair and others), irregular or abnormal ovarian stimulation (Lacassagne and others), and some maternal influence transmitted with the mother's milk (Bittner). (1) Breast drainage may be interfered with as the result of anomalies of the duct, a plug of desquamated cells in the duct, etc. The breast of the typical spinster has an underdeveloped, small, hard, fibrosed nipple, and we have already seen that cancer is commoner in those who have never borne children. According to Adair only 8.5 per cent of patients with cancer of the breast give a normal nursing history. Bagg has shown that in a strain of mice with a low incidence of cancer of the breast, ligation of the ducts to the nipples on one side of the body half way through pregnancy frequently produced carcinoma. By means of very rapid breeding without accompanying suckling he also produced a high proportion of cancer. After all, the animal with the most overworked mammary gland in the world, namely the cow, never develops mammary cancer. (2) The effect of ovarian stimulation can be demonstrated experimentally either by injecting ovarian hormones or by removal of the ovaries. Lacassagne has shown that injection of estrin will produce mammary cancer in mice in a high percentage of cases, even in male mice of a low cancer strain. The preliminary changes are epithelial hyperplasia, dilatation of ducts with the formation of cysts and papillary processes, and round-cell infiltration. Removal of the ovaries in very young mice with a natural high incidence of mammary cancer will prevent the development of cancer in the inactive breasts. It is evident that estrin can act as a carcinogenic agent. The fault may lie not in the ovary but in other ductless glands. There is no evidence that mice of a high cancer strain produce more estrin than those of a low cancer strain. The adrenal cortex acts synergistically with the ovarian hormone, whereas the anterior pituitary acts antagonistically. Adrenal cortical hyperplasia has been observed by Greene and others in animals with spontaneous mammary carcinoma. (3) The importance of heredity in the etiology of cancer is well recognized, but Bittner has shown that in mouse mammary cancer some extrachromosomal influence may be transmitted in the mother's milk. If the young of a high breast tumor stock are suckled by mothers of a low breast tumor stock the incidence of breast cancer is greatly reduced. The exact significance of this startling observation is not yet clear. Bittner

has even succeeded in extracting the cancer-producing factor in the breast of animals with high spontaneous carcinoma of the breast. When this factor was given to animals with a normal incidence of this tumor the incidence rose from 1 per cent to 67 per cent. It seems most probable that the carcinogenic factor is a filterable virus. Wood and Darling report a cancer family in which a number of instances of bilateral mammary carcinoma occurred in the course of four generations. In the third generation three sisters developed breast cancer. The cancer occurred only in those women who had been nursed by their mothers, a fact suggesting the operation of a factor similar to the "milk influence" demonstrated by Bittner in mice. It has been urged that women of families with any malignant tumors in their ancestry refrain entirely from nursing their children.

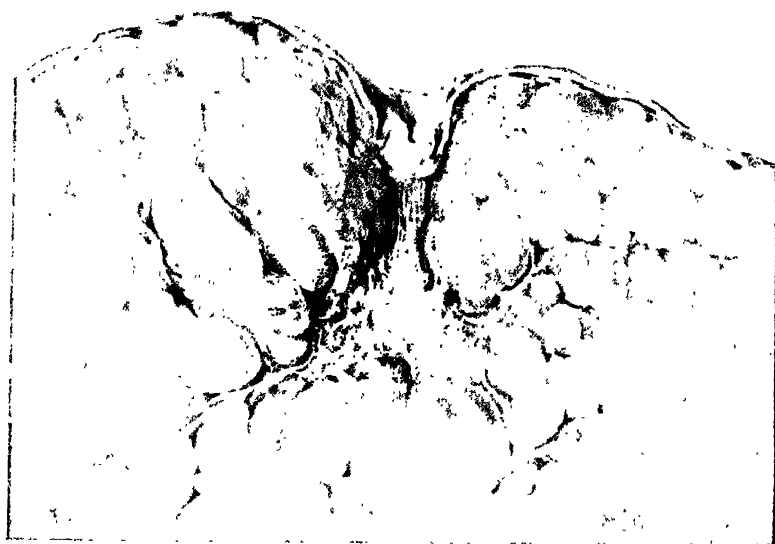
Infiltrating carcinoma may originate *de novo* from normal breast tissue. In many cases, however, there is a preliminary epithelial hyperplasia followed by neoplasia within the ducts before infiltration occurs. This may affect many groups of cells, so that the tumor may be of multicentric origin (Muir). Greene has observed a similar process in rabbits in whom, by means of repeated biopsies, he was able to watch the gradual evolution of the tumor.

Trauma and external irritation bear no relation to cancer of the breast. If trauma were a factor, the disease would be more frequent among the laboring and agricultural classes. That a physical trauma should produce breast cancer is contrary to the dictum that the stimulus to cancer must be of the same type as that to which the particular tissue is biologically best adapted to respond with proliferation.

A great variety of forms of breast carcinoma have been described. Some of the names apply to the gross appearance, some to the microscopic structure, and some to the clinical behavior. The great majority of cases can be placed in one of the following five groups: (1) scirrhus carcinoma, (2) medullary carcinoma, (3) adenocarcinoma, (4) duct carcinoma, and (5) Paget's disease. Rarely the tumor is so undifferentiated that it cannot be placed in any of these groups; this may be called the anaplastic form.

**Scirrhus Carcinoma.**—This is much the commonest form of cancer of the breast. It usually begins in the upper and outer quadrant of the breast, where it forms a hard nodule which can best be appreciated with the palm of the hand. It becomes fixed to the deep fascia and later to the skin, but if the growth occurs midway between fascia and skin the tumor may be freely movable for some time. There may be slight dimpling of the skin due to lymphatic edema. Fixation and retraction of the nipple is a late symptom, caused by involvement of the large milk ducts. The breast is small and flattened. It must be understood that in the early (operable) stage the only sign may be a hard nodule in the breast. Any such nodule in the breast of a woman in the cancer period may be carcinoma, and should at once be examined. Scirrhus carcinoma grows more slowly than the medul-

## PLATE XX



**Carcinoma of Breast**

The concave surface, the indrawn nipple, the infiltration, and the yellowish-grey streaks are all shown.





lary form, but the ultimate prognosis is no better, because though local growth is slow, dissemination occurs early.

The lesion is definitely circumscribed in comparison with cystic hyperplasia, although of course it is not encapsulated and sends processes into the surrounding tissue. It forms a definite *tumor*; an absolutely diffuse lesion is almost certain to be cystic hyperplasia, not carcinoma. It is peculiarly hard, a feature from which it derives its name (*skirros*, hard). It cuts with the grittiness of an unripe pear, so that a diagnosis can often be made the moment the knife enters the tumor. The cut surface is gray, and is seldom homogeneous, present-



FIG. 370. — Scirrhus carcinoma of the breast. The tumor is in the center of the specimen. It is fairly well circumscribed and depressed below the surrounding tissue; the cut surface is marked by streaks.



FIG. 371. — Carcinoma of breast arising from wall of duct.  $\times 145$ .

ing yellow or gray streaks which represent clumps of necrotic fatty tumor cells (Plate XX). The cut surface is concave, retracting below the general level. (Fig. 370.) Small cysts may be present. The gross appearance of a scirrhus cancer is usually so characteristic that the surgeon is able (or ought to be able) to make his own diagnosis at operation without the assistance of a pathologist. When the tumor is exposed it is incised. This is not attended by any danger of dissemination as used to be feared. If the tumor is found to be malignant, radical removal of the breast and the surrounding structures is done at once, whereas if it appears to be benign the entire lump is removed and the diagnosis verified by frozen section on the spot or later paraffin

sections. Prior to operation no surgeon in the world can be certain that a localized lump in the breast is not a carcinoma, however innocent it may appear to be.

The *microscopic appearance* is also readily recognized. The tumor originates from the epithelium lining a duct (Fig. 371), but soon the normal glandular structure becomes replaced by tumor growth, consisting of masses of epithelial cells separated by a dense and abundant fibrous stroma. (Fig. 372.) This may be so dense that the cancer cells are only present in single file, lying within lymph spaces, and in places they may have disappeared completely. The cells are polygonal and distorted by the dense fibrous tissue, they are small and stain darkly, and mitotic figures are rare. Round-cell infiltration may be present in places.

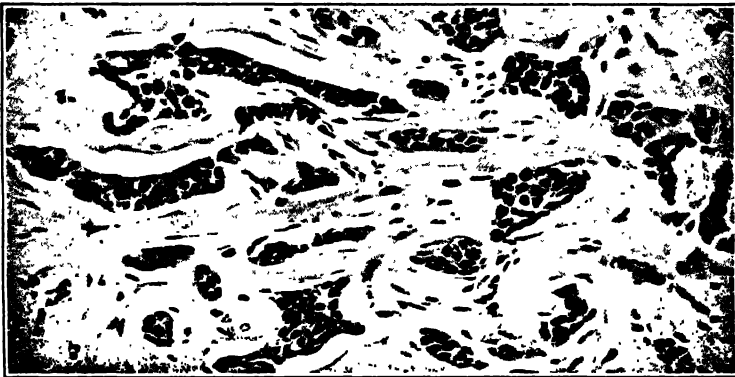


FIG. 372.—Scirrhus carcinoma of the breast. The compressed groups of tumor cells are separated by a dense stroma.  $\times 175$ .

**Medullary Carcinoma.**—This is considerably less common than the preceding form, of which it is merely a variant so that no sharp line can be drawn between the two. The distinction between the two can more readily be made from the gross appearance than under the microscope, for one section may present an *encephaloid* picture while another may be scirrhus in type. The medullary carcinoma does not form the rather early adhesions with the deep fascia or skin which are characteristic of the scirrhus form, and is therefore more difficult to recognize at an early stage. The tumor is soft, rapidly-growing, and is likely to form a bulky local growth which ulcerates the skin. When removed it is soft and friable. It is also called *encephaloid* carcinoma because of its softness, but it seldom resembles brain tissue sufficiently to deserve that name. *Microscopically* the tumor is highly cellular with very little stroma, thus accounting for its softness. The cells, which are large, rounded, and show numerous mitotic figures, are collected in large masses (Fig. 373), but in places there may be some grouping around spaces so as to suggest an attempt at glandular formation.

*Acute carcinoma* is of the medullary type, although usually more diffuse. It generally develops during lactation, and there is rapid dissemination throughout the breast and skin. It is easily mistaken



FIG. 373.—Medullary carcinoma of the breast. The cells are massed together with no stroma between them.  $\times 250$ .

for the acute mastitis which may complicate lactation, for the breast is hot, swollen, painful, and tender, and there is often a well-marked leucocytosis. The course is very acute and seldom lasts more than a few months.



FIG. 374.—Adenocarcinoma of breast.  $\times 125$ .



FIG. 375.—Intraduct carcinoma. The duct is packed with proliferating epithelial cells, but invasion has not yet taken place.  $\times 50$ .

**Adenocarcinoma.**—This is a rare tumor of the breast. It is of soft consistence and may become quite bulky, but it is of slow growth, of

rather low malignancy and may remain localized for a long time. It may finally cause ulceration of the skin and form a large fungating tumor on the surface. The axillary lymph nodes are usually not involved by the tumor, though they may be somewhat enlarged. The microscopic appearance is that of gland spaces surrounded by columnar epithelium. (Fig. 374.) The much commoner duct carcinoma is frequently called adenocarcinoma, but true adenocarcinoma is a rare condition.

**Papillary Carcinoma of Duct.**—This tumor usually arises from one of the large ducts near the nipple, and is commonly called duct carcinoma. The growth may originate from duct papilloma. Owing to fusion of the papillary processes a gland-like condition may be produced, so that the lesion has been called cystadenocarcinoma. The tumor is only slowly invasive. Bleeding from the nipple is a common symptom.

**Intraduct carcinoma** is a convenient term applied to those cases of cystic lobular hyperplasia in which a malignant change is added to epithelial hyperplasia, but the tumor cells are still confined within the walls of the ducts. (Fig. 375.) Such a condition tends to be diffuse in contrast to papillary carcinoma of the main ducts which is a localized lesion. It may be very difficult for the pathologist to decide before invasion has occurred whether such a specimen is malignant or not. The "comedo carcinoma" of Bloodgood (so called because worm-like casts can be expressed from the cut surface) belongs to this group.

**Sweat Gland Carcinoma.**—Ewing, in common with many continental writers, recognizes a sweat gland carcinoma of the breast; indeed, he believes that a considerable proportion of his material belongs to this group. The tumors are said to be especially common in the skin and in the axilla. They are supposed to arise from sweat glands in the breast, which might occur normally or as aberrant inclusions. These are said to be characterized by a special type of epithelium called by the French sweat gland epithelium, by the Germans "pale epithelium," but which we may call eosinophilic epithelium, owing to its red staining. Dawson, in a recent study, considers that this epithelium is derived from normal mammary gland structure, that it does not occur in the normal breast, and that it is only found in cysts, the epithelium of which has undergone proliferation followed by degeneration. Tall columnar eosinophilic epithelium is very common in cystic hyperplasia. In view of the doubt regarding the occurrence of sweat glands normally in the breast, the question of sweat gland carcinoma must be considered to be *sub judice*.

**Paget's Disease.**—The condition described by Sir James Paget in 1874, and since known as Paget's disease of the nipple, is a chronic eczema of the nipple with the development after some years (sometimes as long as ten years) of a cancer in the breast. In the past there has been much difference of opinion as to whether the skin condition or the cancer was the primary lesion. The skin lesion is malignant, but of very slow growth and without glandular involvement. The breast tumor may be of rapid growth. The eze-matous area at the nipple is usually bright red and either moist and weeping or dry and scaly. *Microscopically* the skin in the affected area shows marked

epidermal hypertrophy before ulceration takes place. The most characteristic feature is the presence of the peculiar structures known as Paget cells. (Fig. 376.) These are large, clear, vacuolated cells with small pyknotic nuclei. They look like clear spaces punched out of the epidermis. They are most abundant in the basal layers, but may permeate the entire thickness of the epidermis. The underlying dermis shows infiltration with lymphocytes and plasma cells. In the later stages there is ulceration of the epidermis.

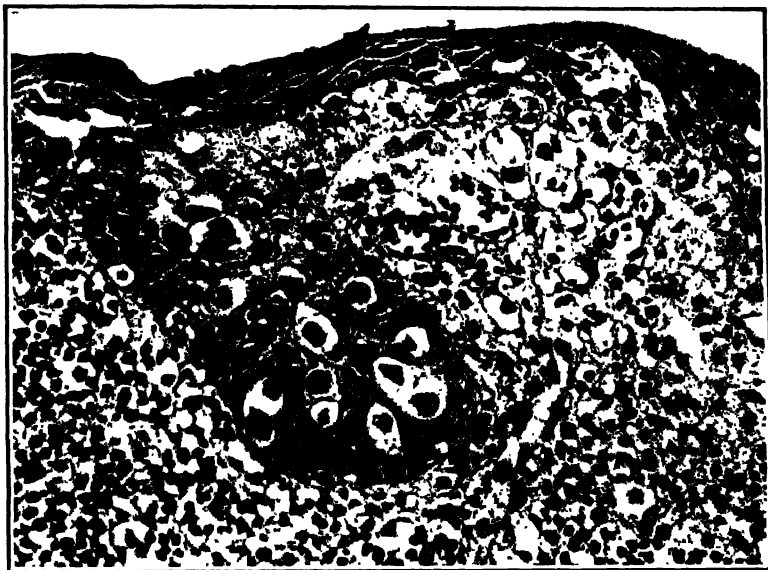


FIG. 376.—Paget's disease of the breast showing clear Paget's cells in the hypertrophic epidermis.  $\times 325$ .

The pathogenesis of the condition is still a matter of dispute. Muir and others believe that it begins as an intraduct carcinoma, and that the cancer cells spread along the duct and penetrate between the cells of the epidermis (intraepithelial spread of carcinoma). Frequently the tumor appears to begin as a local lesion at or near the outlet of a lactiferous duct, whence it spreads centrifugally both in the duct epithelium and in the epidermis, but the continuity is broken when some parts die while others remain alive, so that there may be no connection between the epidermal lesion and the tumor in the breast (Inglis). In such cases Cheatle suggests that the carcinogenic agent has acted both on the epidermis and on the breast tissue at a distance. In support of this is the fact that a series of ducts may show neoplastic change.

**Spread of Breast Carcinoma.**—The cancer cells are spread by infiltration, by the lymph stream, and by the blood stream.

*Infiltration* is the means by which the malignant cells spread throughout the breast. They infiltrate the tissue spaces between the fat cells and connective-tissue bundles, as can be best seen in the scirrhus form of cancer. It is in this way that the deep fascia and skin are involved. Adenocarcinoma and duct carcinoma show a comparatively slight tendency to infiltration. Microscopic sections of the whole thickness of the breast show that the pectoral muscle is involved in over one-half the cases of scirrhus carcinoma at the time of operation, although no gross evidence of involvement may be apparent. This indicates the need of wide removal of the tissues underlying the breast.

*Lymphatic spread* carries the tumor cells to a distance. There are two ways in which this spread may occur. The cells may grow along the lymphatics by a process originally described by Sampson Handley and named by him lymphatic permeation. Or they may be carried by the lymph stream in the form of tumor emboli. It appears probable that embolism is a much more important method than permeation, although for a long time it was thought that permeation was the chief method of spread. The tumor cells reach the axillary lymph nodes early in the disease, especially in the scirrhus form of carcinoma. These nodes show *microscopic* involvement in over 60 per cent of cases at the time of operation. The mediastinal nodes may occasionally be involved quite early, sometimes even before the axillary nodes. It is in these cases that surgery is so helpless. The prognosis depends largely on the question of lymph node involvement. Adenocarcinoma and duct carcinoma rarely invade the nodes, but unfortunately these are uncommon forms of cancer of the breast.

The plexus of lymphatics which lies upon the deep fascia becomes filled with tumor cells, and it is along the planes of the deep fascia and the muscular aponeuroses that the principal spread takes place. The nodules which often appear in the skin after removal of the tumor owe their origin to this deep supply of tumor cells. Obliteration of the deep lymphatics may cause a lymphatic edema of the skin, and as the epidermis is anchored at many points by hair follicles, the intervening skin becomes swollen so as to give a characteristic dimpled appearance known as *pig skin* or *peau d'orange*. The condition spoken of as *cancer en cuirasse* is due to lymphatic edema rather than to invasion of the skin by tumor cells. The pleural and peritoneal cavities may be invaded by lymphatic spread along the fascial and aponeurotic planes. The lung may be invaded from the bronchial lymph nodes, and the liver by way of the lymphatics in the falciform ligament.

*Blood spread* leads to involvement of distant organs. Metastases occur most frequently in the lungs and liver, the next most common locations being the adrenals, spleen and ovaries (Saphir and Morris). It is in the red marrow that the tumor cells lodge, so that metastases are found in the vertebræ, the flat bones, and the proximal ends of the humerus and femur. Spread by the vertebral set of veins (page 258) is probably responsible for involvement of the vertebræ and the skull.

**Prognosis.**—In estimating the prognosis in cancer of the breast, clinical features are of greater value than the microscopic appearance. At the same time we may recognize that the scirrhous and medullary types have a worse prognosis than adenocarcinoma, duct carcinoma, and Paget's disease. The younger the patient and the more rapid the growth, the worse the outlook. Lymph node involvement is the most important factor, as it is an index to the degree of spread. It is difficult to be certain if a patient has been cured, for the disease may recur after a number of years in the mediastinal lymph nodes. The average duration of life in untreated cases is three years. Of patients treated by the radical operation, 50 per cent are alive and well after three years and 30 per cent after ten years. Of patients in whom the disease is still confined to the breast, over 85 per cent are alive and well at the end of ten years. These figures are taken from the report of Janet Lane-Clayton to the British Ministry of Health, based on a most exhaustive investigation.

**Effect of Radiation.**—The radio-sensitivity of cancer of the breast varies markedly with the type of growth. About 20 per cent of the cases are radio-sensitive, 20 per cent are resistant, and 60 per cent are intermediate. Unfortunately radio-sensitivity is no criterion of certain cure. The more sensitive the tumor, the more cellular it must be, and the more cellular the more dangerous on account of the earlier formation of metastases. Scirrhous carcinoma, as might be expected, is highly radio-resistant. The medullary form, on the other hand, may be quite radio-sensitive. Adenocarcinoma and duct carcinoma do not respond well to radiation. The rapidly growing anaplastic forms respond best, but have the worst prognosis.

**Comparison of Lobular Hyperplasia, Fibroadenoma and Carcinoma.**—The recognition of the gross features of the three major diseases of the breast is so important that a brief comparison may be useful. In each of these conditions the patient comes complaining of a *lump in the breast*. Local flattening suggests cancer, local prominence suggests a benign tumor or a cyst. In lobular hyperplasia the lump is best felt with the fingers, in carcinoma it is more easily detected with the palm of the hand, and in fibroadenoma, particularly the pericanalicular type, it is peculiarly mobile. Fixation to the deep fascia and the skin is characteristic of carcinoma, especially the scirrhous form. When carcinoma is squeezed between the finger and thumb there is a wrinkling and dimpling of the skin, which is a pathognomonic and much earlier sign. The *axillary lymph nodes* may be enlarged and hard in carcinoma, small and tender in lobular hyperplasia, and unaffected in fibroadenoma. The *cut surface* of scirrhous carcinoma shows a definite, circumscribed, hard tumor, adherent to the surrounding fat, not encapsulated, gray in color, with a concave surface on which there are yellow streaks and spots; it cuts with the gritty feel of an unripe pear. The fibroadenoma is circumscribed, encapsulated, easily shelled out, firm, but without the dense hardness of a scirrhous cancer; the cut surface is white and homogeneous, although it may be traversed by fine slits. In lobular hyperplasia the cut surface reveals no circumscribed lesion as in most forms of carcinoma, but a diffuse indurated area, tough and india-rubbery in consistence, yellowish-gray in color, and fading away into the surrounding breast; cysts of varying size, sometimes quite large (blue-domed cysts), are commonly visible to the naked eye. Although these various lesions are so different, it must be realized that they may all be produced by the action of ovarian hormones. It is not uncom-

mon, therefore, for one or more of them to be combined. Indeed I have seen carcinoma, duct papilloma, lobular hyperplasia and fibrosing adenomatosis all in one breast.

*Carcinoma of the male breast* is rare. It is usually of a rather high grade of malignancy. Lobular hyperplasia is considerably more common.

**Sarcoma.**—This is also uncommon. It may attain a great size. The cut surface presents a characteristic homogeneous appearance like fish-flesh, and shows none of the yellow necrotic areas and striations characteristic of carcinoma. This, combined with its softness, usually allows a correct diagnosis of the tumor to be made with the naked eye. The sarcoma may develop from a fibroadenoma, in which case it is composed of spindle cells arranged around ducts. In the ordinary form which arises *de novo* it is made up entirely of spindle cells, many of which show mitotic figures. The lymph nodes are seldom involved, but there may be distant blood spread.

*Other tumors* which may rarely be found in the breast are angioma, lipoma, myxoma, and chondroma.

**Bleeding from the Nipple.**—The two common causes of discharge of blood or blood-stained fluid from the nipple are duct papilloma and duct carcinoma. There is much difference of opinion as to whether or not the symptom usually indicates malignancy; but it seems probable that about 50 per cent of the cases are benign and 50 per cent are malignant (Adair). It is important to realize that the discharge may not contain blood although the patient says that it does, and in every case a microscopic examination should be made of a smear. Lobular hyperplasia may cause a discharge from the nipple which is chocolate, green, or yellow in color, but which contains no blood. A dark, stagnant, bloody discharge is practically pathognomonic of duct carcinoma. Transillumination of the breast is useful for localizing the lesion, for a collection of blood appears black with this method.

## CYSTS OF THE BREAST

The common cysts of the breast are those of lobular hyperplasia. These are not retention cysts due to obstruction of the ducts, but are first produced by dilatation from epithelial hyperplasia, followed by incomplete involution which leaves the duct dilated. Obstruction may then be superadded, so that continued secretion may lead to a great increase in size. A feature of these cysts is that the clear fluid which they contain may be under marked tension, so that it spurts out violently when the cyst is incised. A *galactocoele* is a very rare condition in which a large cyst containing milk is formed during lactation. Being a dilatation of one of the main milk ducts, it is situated close to the nipple. *Hydatid cysts* are extremely rare.

## ACUTE MASTITIS

Acute inflammation of the breast is practically confined to the first few weeks of lactation. Physiological hyperplasia may occur immediately after birth and at puberty, and when unduly marked this may cause symptoms which are described clinically as acute mastitis, but it is not a true inflammation. The common infecting organism is the *Staphylococcus aureus*, which produces a localized inflammation. More rarely a streptococcus may cause a diffuse inflammation. Infection takes place through the milk ducts or cracks in the nipple. Suppuration occurs and an *abscess* may be formed. This may be subcutaneous, intramammary, or retromammary. In the latter form the breast is pushed forward. Only one segment of the breast may be



involved, or a number of abscesses may be formed in adjoining lobes so that multiple incisions are required. Acute mastitis may be closely simulated by acute carcinoma, a condition characterized by pain, swelling, heat, and fever.

### OTHER LESIONS OF THE BREAST

**Fat Necrosis.**—It has long been known that a quiet necrosis with saponification may occur in traumatized or ischemic fat in any part of the body, a process similar to pancreatic fat necrosis but of slower *tempo* due to absence of the active pancreatic lipase. Within recent years it has been recognized that such a process in the breast may give rise to a lesion which closely simulates scirrhus carcinoma (Lee and Adair). A history of trauma to the breast shortly before the appearance of the lesion is obtained in many cases, so that the condition is commonly called traumatic fat necrosis, but in about one-half the cases there is no such history. The patients are usually corpulent with large full breasts, and most cases occur in the fourth and fifth decades. A hard localized mass is formed, which is often adherent to the skin, so that the condition is readily mistaken for cancer.

The *gross appearance* of the lesion is characteristic, and should be recognized in the operating room. The affected area is of an opaque, white, chalky appearance, which is well shown in one of Hadfield's illustrations. This area is composed of necrotic fat. As saponification proceeds liquefaction takes place, and a cavity is formed containing a pool of yellow oily fluid. This pseudocyst is surrounded by dense tissue which represents a reaction to the fatty irritant. Lime salts combine with the liberated fatty acids, so that some degree of calcification is common. The cicatricial contraction, the concave surface, and the yellow streaks of scirrhus carcinoma are absent.

The *microscopic appearance* is similar to that of fat necrosis elsewhere in the body. The fat cells are broken into droplets which remain attached to the cell envelope and stain faintly with hematoxylin. Fatty acid crystals may be present. The surrounding tissue shows a chronic productive inflammation, and contains large numbers of phagocytic cells filled with lipid material. Foreign body giant cells form a striking feature of the lesion. Lymphocytic infiltration and an obliterating endarteritis complete the picture.

**Plasma Cell Mastitis.**—This rare condition is an acute or subacute inflammation not associated with lactation but with the clinical signs of malignancy. It begins suddenly with pain, tenderness, diffuse swelling, and enlargement of the axillary lymph nodes. The acute symptoms soon subside, leaving the breast hard, the skin adherent, and the lymph nodes larger and firm, so that to mistake it for carcinoma is almost inevitable. The gross appearance is that of a hard diffuse mass, while microscopically there are polymorphonuclears, lymphocytes and plasma cells. The latter may predominate and form solid masses, giving the condition its name.

**Tuberculosis.**—Tuberculosis of the breast is uncommon but not rare. At first it takes the form of a hard mass, which is easily mistaken for carcinoma. Softening occurs, with the formation of large tuberculous cavities and sinuses opening on the surface. The microscopic picture is characteristic of tuberculosis.

**Syphilis.**—Syphilis of the breast is rare. There may be a primary lesion (chancre) of the nipple, and secondary mucous patches may occur. The most important lesions are the tertiary ones, for they are liable to be mistaken for carcinoma. There may be a localized gumma, or a diffuse inflammatory infiltration causing widespread induration very chronic in character, and offering great diagnostic difficulty, for there is nothing really characteristic about the microscopic appearance.

**Actinomycosis.**—This is one of the rarest of breast diseases. It may involve the breast by extension through the chest wall from the pleura.

**Hypertrophy.**—Hypertrophy of the breasts usually comes on soon after puberty, but may occur during pregnancy or lactation. It is probably of endocrine origin, due to some abnormal action of the ovarian hormone. The hypertrophy involves both glandular and connective tissue, but as a rule most of the enlargement is due to a great increase of the connective tissue, which is soft and of open structure.

**Congenital Anomalies.**—*Amastia* or congenital absence of the breast is usually bilateral but may be unilateral. *Athelia* or absence of the nipple is rare. It may be associated with *anastia*, or the breast may be well developed. *Polymastia* or abnormal number of breasts is much more common than either of the preceding conditions. The "milk-line" extends from the axilla to the groin, and accessory or supernumerary breasts may occur anywhere along this line, the most common site being the axilla. The accessory mammary tissue may or may not be provided with a nipple. The mass enlarges during lactation and may secrete milk. *Polythelia* or accessory nipples are rare. They may occur on the breast or elsewhere along the milk-line. In the latter case they have underlying mammary tissue (*polymastia*).

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## CHAPTER XXVIII

### THE DUCTLESS GLANDS

In this chapter the diseases of the ductless glands will be considered. There are no organs in the body in which it is so difficult to correlate changes in function with changes in structure as the members of the endocrine system, for the reason that our knowledge of their function is still so meager and vague. We shall therefore have to be content with describing the lesions found in disease and the disturbances produced by altered function without much attempt at correlating the two. The ductless glands are the chemical regulators of the body by virtue of the hormones (*hormao*, to excite) which they produce. The hormones govern the processes concerned with growth, metabolism, and reproduction. Of special importance in pathology is the fact that some of the hormones control the metabolism of certain inorganic elements, and that upset of this control may have serious effects. Thus the adrenal cortex controls sodium metabolism, the thyroid iodine metabolism, and the parathyroids the metabolism of calcium and phosphorus.

**Interrelationships.**—The ductless glands are members of the endocrine system, but they are also “members one of another,” for at least some of them exert an important influence upon other members of the series. It would indeed be rash for a mere pathologist to venture forth on the uncharted sea of the endocrines, strewn as it is with the wrecks of shattered hypotheses, where even the most wary mariner may easily lose his way as he seeks to steer his bark amid the glandular temptations whose siren voices have proved the downfall of many who have gone before. And yet the fact that the ductless glands do form an interrelated system cannot be passed over in silence. The best example of interrelationship is the action of the anterior lobe of the pituitary on the ovary. The anterior pituitary and thyroid also work together. Removal of the anterior pituitary interferes with the development of the thyroid and also prevents the normal thyroid hyperplasia which follows removal of part of that gland, while pituitary implants restore this power.

If one ductless gland influences another it may be either in the direction of stimulation or inhibition. If this influence becomes exaggerated, the resulting effect will be of a mixed type due to excess or deficiency in the internal secretion of two members of the series. In this way the so-called polyglandular syndromes may arise.

The relation of the anterior lobe of the pituitary to the ovary has already been discussed in connection with gynecological pathology, and will be referred to again later in this chapter. It affords an example

of a physiological relationship under normal conditions (action of anterior pituitary on ovary) and of a pathological relationship (Fröhlich's syndrome or failure of sexual development in pituitary disease). The adrenal cortex evidently has a marked influence on the gonads, because tumors of the adrenal cortex are associated with premature sexual development in boys and virilism in the female. The adrenal seems to be concerned with the male side of development and the pituitary with the female side. It appears that with respect to endocrine organization the female is essentially a hermaphrodite in whom the masculine component is never extinguished but merely quiescent. For this reason virilism in the female is always more striking than femininity in the male.

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### THE ADRENALS

**Descriptive Outline.**—The right adrenal is triangular like a cocked hat, the left is crescentic. The weight is 5 to 6 grams. The cut surface shows cortex and medulla. The cortex is much more abundant; indeed in many sections no medulla can be seen. The outer part of the cortex is light yellow owing to the abundant lipoids it contains, the inner part (*zona reticularis*) is dark brown and often shows softening or cavitation at autopsy. A very common error is to mistake this inner layer for the medulla, especially when there happens to be no medulla in the slice inspected. The medullary tissue is white or gray, and may sometimes be seen adhering to the wall of a cavity in the *zona reticularis*. It is stained brown by immersion in a solution of a chrome salt (chromaffin reaction).

**General Considerations.**—The adrenal is two organs in one, for the cortex and medulla are different in origin, structure and function, and in the lower animals they remain separate. The *cortex* is mesodermal in origin, arising from the Wolffian ridge in conjunction with the sex glands, but becoming separated from the latter by their descent into the pelvis. The cortex exercises an important influence on the development of the sex glands, for cortical tumors cause a marked increase in masculine features (virilism) in both sexes, and pseudo-hermaphroditism in the female (female gonads associated with male external genitalia) is commonly associated with enlargement of the adrenals due to cortical hyperplasia. Accessory cortical tissue is common at birth, but it soon atrophies and disappears. Occasionally it may persist into adult life as small bright yellow nodules which are found under the capsule of the liver and in the line of descent of the sex glands, *i. e.*, in the kidney, along the line of the spermatic vein, in the broad ligament, testicle, and ovary. The yellow color of

the cortex is due to the large amount of lipoid (cholesterol ester) which it contains. This is increased during pregnancy and lactation. There is marked disappearance of the lipoid in acute infections, and to a lesser degree in anemia and severe hemorrhage.

The *medulla* is ectodermal in origin, arising from the neural crest together with the anlage of the sympathetic nerve cells. It forms part of the chromaffin system, staining brown with chrome salts (potassium bichromate), together with the abdominal sympathetic, the carotid body, and the organ of Zuckerkandl (a small body at the bifurcation of the aorta in children).

The *development* of the adrenal glands presents some singular features. In fetal life the adrenal is almost all cortex, and at the third month it is actually larger than the kidney. The fetal cortex is different from the cortex after birth (usually called adult cortex), for it contains no lipoid and is arranged in sheets instead of columns. At birth there is a thin layer of cortex of the adult type and a very thin core of medulla. The weight compared with the kidney is about 1 to 3.5. In the adult it is 1 to 30. Immediately after birth a strange change takes place. The entire fetal cortex rapidly degenerates, and is slowly replaced by adult cortex and medulla, but it is not until the twelfth year that the original size of the adrenal gland at birth is regained. The cortex is not entirely of the adult type until the end of the first year. Massive hemorrhage may occur into the degenerating cortex at birth, and as the hemorrhage is often bilateral it may prove fatal to the child. It is possible that the cortical necrosis and perhaps also the hemorrhage are due to sudden withdrawal of the female sex hormone with which the fetal tissues have been bathed during pregnancy, just as the endometrial necrosis and hemorrhage of menstruation are caused by sudden withdrawal of the corpus luteum hormone. In the *anencephalic fetus* the fetal cortex is absent, so that the adrenals are very atrophic. This maldevelopment of the adrenals is probably the result of interference with the development of the pituitary, for in anencephalic monsters the posterior lobe of the pituitary is often missing (Angevine).

The *physiology* of the adrenal glands must be of the greatest importance, but our knowledge of the subject is amazingly limited, what little we know coming from pathological observations rather than from physiological experiment. The most important and certain fact is that removal or destruction of both adrenals is invariably followed by death. It is the loss of the *cortex*, not the medulla, which proves fatal and cortical extract can preserve the life of adrenalectomized animals indefinitely. Cortin is the extract made from the adrenal cortex; desoxycorticosterone is a synthetic product with an identical hormonal action. The cortex controls sexual development. About the sixteenth week of development a layer in the fetal cortex stains red with fuchsin in the Mallory connective-tissue stain. This has been called the androgenic or masculinizing layer, because fuchsin-staining cells are associated with virilism (Vines). Virilism in women may have its basis in the pituitary, the adrenal or the ovary. The essential pituitary change is a peculiar hyaline degeneration of the basophils of the anterior pituitary; normally these cells seem to inhibit activity of the androgenic cells which already exist in the ovary, an organ that is bisexual. Virilism may be caused by increase in the number and activity of the fuchsinophil cells in the adrenal cortex. Finally it may be due to an ovarian arrhenoblastoma. For further information regarding the adrenal cortex and intersexuality the monograph by Broster and Vines should be consulted. Hypofunction of the cortex is associated with the appearance of Addison's disease. A function of supreme importance is the control of the permeability of membranes, and in consequence the distribution of the inorganic ions, sodium, potassium and chloride, and also of water. There is

invariably a disturbance of this function in adrenalectomized animals and in Addison's disease. It would appear also that the adrenal cortex produces substances which are necessary for recovery from the effects of harmful physical and chemical stimuli and from a state of shock.

The *medullary* secretion is not essential to life. This is natural, seeing that the rest of the abdominal chromaffin tissue can probably take on the function of the medulla. Most of the experimental work has been done on the medulla, because a powerful extract (adrenalin, epinephrin) was early obtained from this part of the gland. This stimulates all structures innervated by the sympathetic nervous system, the action taking place at the myoneural junction. According to Cannon's emergency theory, the medullary secretion is needed for adjusting and reinforcing the bodily mechanisms in times of demand such as anger, combat and flight when arterial contraction and the immediate conversion of glycogen into fuel are needed, but it has little to do in normal times of quiet. It hardly seems reasonable to suppose that this is the sole function of the medulla.

### ADRENAL INSUFFICIENCY. ADDISON'S DISEASE

This disease is of great historical interest, because Addison's demonstration that the syndrome of progressive weakness, pigmentation of the skin, and gastro-intestinal disturbance was due to lesions of the adrenals was the first indication that constitutional disease could be caused by lesions of a ductless gland, and thus formed the starting-point of the entire subject of endocrinology.

**Symptoms.**—The characteristic asthenia is gradual in onset, the heart's action is feeble, the blood-pressure remarkably low. The gastro-intestinal symptoms are nausea, vomiting, and attacks of diarrhea. The pigmentation, which ranges from light yellow to deep brown, is most marked on exposed parts and in regions where normal pigmentation is well marked (areola of nipples, genitals, etc.). The mucous membranes of the mouth and vagina are often pigmented. When the patient is put on a chloride-free diet and given potassium there is a large excretion of chlorides in the urine, whereas in a normal person under similar conditions it is quite small. Although the downward course is generally gradual, there may be remissions and exacerbations. The latter are known as *crises*, and are marked by extreme arterial hypotension, decrease in the blood volume, gastro-intestinal symptoms, and shock, sometimes terminating in sudden death. Hypoglycemia is apt to develop, and death may be due to hypoglycemic shock. An important function of the adrenal cortex is regulation of the water and sodium chloride balance, so that in Addison's disease loss of sodium and chlorides and water is a striking feature, and many of the symptoms are relieved by the administration of salt. Estimation of chloride excretion in the urine is a valuable test. There is retention of potassium in the blood, probably due to a change in the permeability of cell membranes and consequent disturbance of potassium exchange. The blood urea is frequently increased, due apparently to failure in renal function caused by fall in glomerular filtration pressure.

**Lesions.**—The lesions of the adrenals (always bilateral) may be of three varieties: tuberculosis, atrophy, and secondary tumors. (1) Of these *tuberculosis* is by far the most common. (Fig. 377.) It is of the chronic fibrocascous type. The patient seldom shows clinical evidence of tuberculosis, and it may be difficult to find the primary lesion which is the cause of the infection. Both cortex and medulla are destroyed, but a small portion of cortex always remains, otherwise life could not

have been supported. The disease is confined to the adrenals and the kidneys are not involved, nor does renal tuberculosis spread to the adrenals and cause Addison's disease. (2) *Simple atrophy* (so-called) is a necrosis of the adrenals rather than an atrophy, although all trace of the active process may have been lost. It is apparently very much commoner than it used to be. Duffin found necrosis to be the causal factor in 41 per cent of the cases studied in my department. Many of these patients (male) have scanty hair on the face and body, a feature which makes it possible to prophesy that necrotic atrophy will be found in such cases. The adrenal glands are very small, and



FIG. 377.—Addison's disease. Enlargement of the adrenal the result of caseous tuberculosis.



FIG. 378.—Atrophy (necrosis) of the adrenal cortex.  $\times 250$ .

usually show marked lymphocytic infiltration. (Fig. 378.) In some cases only the cortex is affected by the atrophy, the medulla remaining intact. Wells, comparing this necrosis with the acute yellow atrophy of the liver produced by cinchophen and the selective destruction of marrow elements by aminopyrin, etc., resulting in agranulocytosis, suggests that the adrenal atrophy may be due to one of the newer drugs in those who have an idiosyncrasy for it. (3) *Bilateral tumor formation* is a rare cause. The tumor is usually a secondary carcinoma. In rare cases primary carcinoma of the cortex on both sides has given rise to the picture of Addison's disease. An apparently constant change

is extreme reduction in the number of basophil cells in the anterior pituitary (Crooke and Russell).

**The Relation of Symptoms to Lesions.**—On account of our ignorance regarding the normal physiology of the adrenal cortex and medulla, it is impossible to suggest a reasonable correlation between the symptoms of the disease and the lesions in the adrenal glands. The low blood-pressure and muscular asthenia are probably due to deficiency of cortex rather than medulla as used to be thought, for the administration of adrenalin is without marked benefit, whereas Swingle's cortical extract may bring the blood-pressure back to normal and restore the muscular power. The sodium concentration of the blood is decreased owing to increased sodium excretion, which in turn is due to destruction of cortical tissue. This diagnostic change in the sodium level is most marked when salt is withheld, but such withdrawal may precipitate dangerous adrenal crises. The administration of salt will often alleviate acute adrenal insufficiency. The cause of the gastro-intestinal disturbances is quite obscure. The question of the pigmentation in Addison's disease has already been discussed in Chapter II. The pigment is melanin, and is found principally in the basal cells of the epidermis. The pigmentation is therefore a form of melanosis. Melanin is normally formed in certain epithelial cells named melanoblasts as the result of an interaction between a specific ferment in these cells and a colorless chromogenic mother substance, melanogen, which the cells take up from the blood. Adrenalin seems to be formed from melanogen by the cells of the adrenal medulla. It is possible that when the adrenal is no longer able to utilize the melanogen, this substance accumulates in the epithelial cells of the skin and mucous membranes, and is there converted by the specific ferment into melanin, with pigmentation as a result. This is merely a guess, but so far no better one has been suggested.

**Acute Adrenal Insufficiency.**—Destruction of both adrenal glands may give rise to a fatal insufficiency which is acute instead of chronic in type. The clinical picture may be of an acute abdominal type, with severe epigastric pain, vomiting and shock; of a cerebral type with convulsions and coma; or of an asthenic type which ends fatally in a few days. In most cases the lesion is a hemorrhage or thrombosis which quickly destroys both the glands. In others the lesion may be chronic, *e. g.*, tuberculosis. No explanation can be given of the acute picture in such cases. It is probable that if the sodium concentration of the blood were to be measured it would be found to be markedly decreased.

### TUMORS OF THE ADRENAL GLAND

Adrenal tumors are rare in comparison with the relatively common hypernephroma of the kidney. Although the cortex is of mesoblastic origin, its cells are epithelial in type, so that the cortical tumors are adenoma or carcinoma. The medulla is composed of nerve cells and belongs to the chromaffin system, so that a medullary tumor may be a neuroblastoma, ganglioneuroma, or chromaffinoma.

**Cortical Tumors.**—**Adenoma.**—Small hyperplastic nodules about the size of a pea composed of normal adrenal cortex are quite common. They do not deserve the name of adenoma. Larger masses of typical or atypical structure form more definite tumors. They are quite rare. The tumor cells are occasionally filled with yellow pigment similar to that seen in chromaffin cells, thus producing a sharp contrast between the neoplasm and the surrounding cortical cells.

**Carcinoma.**—This uncommon tumor resembles the hypernephroma of the kidney in its gross appearance. It is yellow in color, often hemor-



rhagic, and may attain a large size. (Fig. 379.) Not infrequently it is bilateral. The microscopic picture varies in its degree of differentiation. Some cases are distinguished with difficulty from an adenoma, the acini and columns of the cortex being fairly well reproduced; although appearing rather benign, they may be quite malignant clinically. Others may be called malignant adenoma; a suggestion of acinar grouping still remains, and the cells are large and contain lipoid, but the arrangement is quite atypical and the picture evidently carcinomatous. Giant cells may form a marked feature. In a third group the structure is anaplastic, consisting of solid cords of small dark cells. Sometimes sarcomatous characters are evident in adrenal carcinoma, the cells being fusiform and arranged diffusely. Such a picture recalls the fact that the cortex is mesoblastic in origin. Some workers (Broster and Vines, Goormaghtigh) state that the masculinizing tumors present cells containing fuchsinophil granules similar to fuchsinophil cells in the so-called androgenic juxtamedullary zone of the cortex which is large at birth but small in adults. An excellent colored illustration of fuchsinophil cells will be found in Karsner's Human Pathology.

The tumor may *spread* widely. The adrenal disappears and the kidney may be involved, so that difficulty may arise in distinguishing the tumor from a hypernephroma. This can be done by remembering that in the latter condition the adrenal is usually intact.

The adrenal and renal veins are invaded, and the tumor may grow along the renal vein into the vena cava. The opposite adrenal is often affected, and metastases are common in the retroperitoneal, mesenteric and mediastinal lymph nodes, and in the liver, lungs, brain, and other organs. The bones are seldom involved; in this respect the tumor differs markedly from hypernephroma.

The *symptoms* throw light on the function of the adrenal cortex. In children the tumor is five times commoner in girls than boys (Glynn), but in adults it is equally common in both sexes. The affect of the



FIG. 379.—Carcinoma of the adrenal. The tumor is entirely confined to the adrenal, and has not invaded the kidney.

tumor in children is to produce precocious development of the sexual organs with an intensification of maleness, a condition known as *adrenogenital syndrome*. In girls there is a development of both primary and secondary male characters. The clitoris becomes enlarged, and hair appears on the face and body, a condition known as *hirsuties*. In boys there is marked premature development of the sex organs, which is frequently associated with impotence. In women the sex organs atrophy, amenorrhea and obesity develop, the voice is deep, and there is marked growth of hair on the face and upper lip. The clinical symptoms have been collected into two groups, the Cushing syndrome and the adrenogenital syndrome. The *Cushing syndrome*, similar to that produced by basophilic adenoma of the pituitary, is characterized by muscular weakness, hirsutism, amenorrhea or impotence, atrophy of skin and osteoporosis, occasional hypertension, and diabetes without response to insulin. There is nearly always a characteristic hyaline change in the basophilic cells of the pituitary, the granules of which disappear (Crooke). The *adrenogenital syndrome* shows hirsutism, virilism, increased muscularity, but seldom diabetes. Adult males show no sexual change, except in rare cases where the tumor produces a feminizing change. In these instances the urine contains estrogenic material. Hypertension is often present, and may be paroxysmal in type. In a young woman with a large adrenal cortical tumor and persistent hypertension I found marked nephrosclerosis with the usual arterial changes. If the adrenal tumor can be removed, all evidence of virilism may disappear and the blood-pressure may fall to normal. It is evident that one form of arterial hypertension can be caused by overactivity of the adrenal cortex.

Adrenal cortical tumor is one of the few conditions other than pregnancy in which an easily detectable abnormality can be found in the hormonal activity of the urine. A good index of androgenic activity of the urine is afforded by a color reaction, which is given by 17-ketosteroid compounds (steroids with a ketone group on the 17th carbon atom), among which are androsterone and dehydroandrosterone which form the main androgenic constituents of the urine. The test is referred to as the 17-ketosteroid test. The normal figure is from 10 to 20 mg. per twenty-four hours in the male and 5 to 15 mg. in the female. In cases of adrenal cortical tumor the figure is usually over 200 mg. in twenty-four hours. It may be noted by way of contrast that in Addison's disease the 17-ketosteroid excretion falls practically to zero. These facts suggest that the adrenal cortex may be the chief source of androgenic material in the urine.

**Medullary Tumors.**—The primitive sympathetic neuroblasts which form the anlage of the adrenal medulla develop either into nerve-ganglion cells or into chromaffin cells (pheochromocytes). Three types of tumor may thus arise from the medulla: (1) the *neuroblastoma*, from the primitive neuroblasts; (2) the *ganglioneuroma*, from the mature ganglion cells; (3) the *chromaffinoma* or pheochromocytoma (*phaios*, dark), from the chromaffin cells. The first is much the

commonest (although itself rare), and being primitive in type is highly malignant. The other two arise from adult cells and are innocent.

**Neuroblastoma.**—The tumor is confined to children, usually under four years of age. It is soft and may grow to a great size. Often it is bilateral. Occasionally it does not arise from the adrenal, but from sympathetic nerve tissue in the abdomen or thorax. The microscopic picture resembles that of a sarcoma, and formerly this tumor used to be called "adrenal sarcoma of children." Most of the so-called retro-peritoneal round-cell sarcomas of infants are of this character, arising from the abdominal sympathetic ganglia. The tumor consists of undifferentiated small round cells (neuroblasts), a few imperfect ganglion cells, and fibrils. The fibrils form the distinctive feature, for they are nerve fibrils and are arranged either in longitudinal bundles or in little rounded masses around which the cells are grouped in a "rosette" form. (Fig. 380.) These rosettes are highly characteristic of the tumor, but sometimes they are found with difficulty.

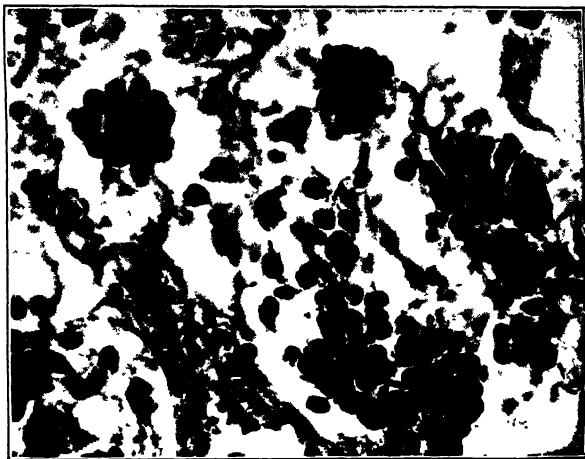


FIG. 380.—Neuroblastoma showing rosettes.  $\times 400$ .

*Spread* of the tumor often gives rise to the formation of remarkable metastases in the skull, particularly in the orbit, so that the first sign of the disease may be the appearance of a hemorrhagic area in the neighborhood of the eye, followed later by protrusion of the eyeball (proptosis). When proptosis develops in a young child it is well to examine the abdomen. Other bones besides the skull may also be involved. This picture is referred to as the Hutchinson type. It seems likely that spread to the skull takes place by the vertebral system of veins (page 258). In other cases there is a great and uniform enlargement of the liver due to diffuse infiltration with liver cells. The mesenteric nodes are involved. This is spoken of as the Pepper type. It is natural that tumor cells should spread more readily to the liver from the right than from the left adrenal, but there is little justification for

the common statement that the Hutchinson type indicates a left adrenal tumor, the Pepper type a tumor in the right adrenal.

Although neuroblastoma is so malignant a tumor, not all cases are progressively fatal. Incredible though it may sound, recovery may take place either spontaneously or following radiation (Farber). In one case at the Toronto Sick Children's Hospital part of the tumor was removed but the remainder had to be left in the abdomen, yet the child made an uninterrupted recovery, and was alive and well four years later.

**Ganglioneuroma.**—This rare form of innocent tumor occurs both in children and adults, and is found in the brain and abdominal sympathetic as well as in the adrenal medulla. It is composed of adult ganglion nerve cells, spherical or pyramidal, and nerve fibers which may be medullated or non-medullated.



FIG. 381.—Pheochromocytoma. The large ragged cells resemble those of adrenal medulla.  $\times 320$ .

**Pheochromocytoma (Pheno, dark).**—This rare tumor is also known as chromaffinoma and paraganglioma. It is usually innocent, small, well encapsulated, and may be found by accident at autopsy in elderly persons. Several cases which I have studied have presented a characteristic cystic degeneration. The tumor may be brown in color. About 20 per cent of the cases are said to be bilateral, and these are usually malignant. Occasionally it may attain a great size, as in one case reported by Soffer and his associates where the tumor weighed 2000 grams. The most interesting clinical feature is the frequent occurrence of arterial hypertension, usually paroxysmal in type, for the tumor contains a large amount of adrenalin, often much more than the normal adrenal, and a pressor substance can be demonstrated in the blood. During the attacks the systolic blood-pressure may rise to 250 or even 300 mm. of mercury, and an accompanying hypoglycemia may lead to shock. The

attack may last for minutes or hours, and if prolonged it may prove fatal. The tumor may be demonstrated radiographically by perirenal insufflation or by depression of the renal pelvis in a pyelogram. As the result of an attack the patient may pass into a state of shock, which may prove fatal. These tumors are found in other parts of the chromaffin system, such as the carotid body, the abdominal paraganglia and the organ of Zuckerkandl at the bifurcation of the aorta. It is best to use the name chromaffinoma for the whole group, pheochromocytoma for the adrenal tumors, and paraganglioma for the extra-adrenal tumors. The tumor is composed of large epithelium-like cells (Fig. 381) which are often pigmented and may stain brown when fixed in chrome salts. In a number of cases there has been an associated neurofibromatosis.

*Secondary tumors* are quite common in bronchogenic carcinoma and are frequently bilateral; much less often they are due to cancer of the breast and other organs. They are usually in the medullary portion. Bilateral tumors may in rare instances cause Addison's disease.

### DEGENERATIONS OF THE ADRENAL GLANDS

Postmortem change in the adrenal glands is extremely common, and must not be mistaken for evidence of disease. The inner layer of the cortex softens, and is converted into a brown mush, so that only a rind of cortex is left. Focal necrosis of the cortex may be caused by infections and intoxications, and hemorrhage is common in diphtheria. Massive hemorrhage is rather frequent in the newborn, and when bilateral it may be a cause of death. The hemorrhage follows the necrosis of the inner layer of the cortex which always occurs at birth, possibly as the result of the sudden withdrawal of the female sex hormone. Fatal massive hemorrhage is not confined to this age. It is apt to occur in meningococcal septicemia, and the combination with this infection and massive bilateral adrenal hemorrhage is known as the *Waterhouse-Friderichsen* syndrome. The cortical lipid disappears quickly in acute infections, more slowly in chronic infections and anemia, and is increased in arteriosclerosis, chronic nephritis, and nephrosclerosis. Amyloid degeneration affects the adrenal at the same time as the liver, spleen, and kidney, with enlargement and hardening of the gland.

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## THE THYROID GLAND

**General Considerations.**—The thyroid gland is one of the most labile organs in the body. It is continually being played upon by various influences (endocrine, etc.), and responding to the varying demands of thyroxin. On this account the structure is not fixed, any more than the structure of the breast or endometrium is fixed. Physiological variations as evidenced by a certain amount of hyperplasia and involution are common in autopsy specimens, although in some cases no doubt they are terminal. Such compensatory hyperplasia is not necessarily associated with any symptoms of hyperthyroidism. The pathological thyroid gland differs from the normal in degree rather than in kind of change, and it is often extremely hard to draw a line between the two. It may well be that under normal conditions the acini of the thyroid are in various phases of function, which may be called the resting, secretory and resorptive phases (Halpert). In the resting phase the acini are large, lined by flattened cells, and filled with deeply stained homogeneous colloid. This is the picture in colloid goiter and in the gland of hyperthyroidism treated with a solution of iodine. In the secretory phase the acini are lined by cuboidal epithelium and the colloid is stained moderately darkly. This is the picture seen in the normal thyroid. In the resorptive phase the acini are lined by columnar epithelium, and contain lightly stained, vacuolated and scalloped colloid. This is the picture seen in hyperthyroidism and in patients treated with thiouracil. The normal thyroid gland in non-goitrous districts weighs from 25 to 35 grams, but it weighs more in women than in men, more in the summer than the winter, more during pregnancy and lactation, and more in goitrous districts even though it may appear to be quite normal.

The chief function of the thyroid gland is to maintain a higher rate of metabolism, as evidenced by heat production, than would otherwise be possible, and to regulate this rate according to the needs of the body. This is done by means of its iodine-containing hormone, thyroxin. The physiological effect of feeding thyroid gland is to raise the rate of metabolism. Removal of the thyroid gland is followed not only by a loss of heat production, but in the growing animal by poor physical, mental and sexual development. The thyroid gland has a remarkable affinity for iodine, and is the only organ in the body which has the power of storing that element. The iodine content of a dog's thyroid can be increased several hundred per cent in the space of five minutes by the intravenous injection of 50 mg. of potassium iodide. The rapidly stored iodine is at first inactive, but gradually becomes converted into an active form. The active principle of the gland contains 65 per cent of iodine. Apparently the iodine is converted by the epithelium of the acini into thyroxin. Some of this passes into the circulation in response to the demand of the tissues. The rest is stored in the form of colloid within the acini, where it constitutes an emergency ration which can be used when the need arises. The normal iodine content of the gland is about 0.2 per cent. If it falls below 0.1 per cent morphological changes at once become apparent in the acinar epithelium, and the gland becomes enlarged in consequence. This fall may be due to an increased

demand on the part of the tissues for thyroxin, or to an inadequate supply of iodine to the gland. The morphological changes are hypertrophy and hyperplasia of the acinar epithelium together with an increased vascularity. As a result of this cellular activity the emergency ration in the colloid is made use of and depleted, and the demand of the tissues for thyroxin is met. If this demand is moderate the hypertrophy may be regarded as physiological; when it is excessive or long-continued the response of the thyroid becomes pathological. When the iodine supply is insufficient the epithelial activity is an indication that the gland is engaged in the attempt to make bricks without sufficient straw, and if the strain is not too great the attempt may be successful. The administration of iodine, even in minute doses, soon relieves the strain, and the epithelial activity subsides, while the iodine-containing colloid collects once again within the acini. The process is known as involution.

In dogs and in other experimental animals the process of hyperplasia is diffuse, so that there is a uniform enlargement of the the entire gland. In man, on the other hand, it tends to be patchy and localized, with the result that nodules tend to be formed. These are known as adenomas, although in the great majority of cases they are not true tumors, so that the name is misleading. Some of these nodules or adenomas respond to iodine treatment like the rest of the gland, but others may not.

An intimate relationship exists between the thyroid and the anterior pituitary, a mechanism which has been called the pituitary-thyroid axis. The thyrotropic hormone of the pituitary is the most powerful known stimulant of thyroid activity. In the experimental animal it causes extreme enlargement of the gland, great epithelial hyperplasia, and corresponding elevation of the basal metabolic rate. The pituitary itself is under the influence of nervous stimuli from the hypothalamus, the controlling center of emotional activity. It is evident that emotional disturbance may be expected to play a part in thyroid hyperactivity. The thyrotropic hormone is also responsible for the exophthalmos which accompanies Graves' disease. Here the action appears to be through the cervical sympathetic on the orbital tissues. There is a two-way traffic on the pituitary-thyroid axis, the thyroid hormone inhibiting the production of the thyrotropic hormone, so that in health a balance is maintained.

Certain sulphur-containing substances cause a curious dissociation of the usually associated thyroid hyperplasia and increased basal metabolic rate, stimulating the former and depressing the latter. Chief amongst these are the sulphonamide drugs and sulphur-containing thiourea and its non-toxic derivative thiouracil. They appear to prevent the synthesis of thyroxin at a normal rate, the accompanying thyroid hyperplasia being an attempt to compensate for this defect. Iodine, on the other hand, when given to control the thyrotoxicosis of Graves' disease, appears to push the finished product into the warehouse (thyroid follicles), and thus prevent free distribution of thyroxin to the body. The two groups of agents thus act at different points of the hormone assembly line (Means).

**Goiter.**—This is an indefinite term applied to enlargement of the thyroid. From what has been said it is evident that theoretically this enlargement might be evidence: (1) of a primary hyperplasia; (2) of a compensatory hyperplasia to meet increased demands of the tissues for hormone; and (3) of increased storage of colloid.

There is no satisfactory *classification* of goiter. It is usual to recognize three main types: diffuse colloid goiter, exophthalmic goiter (Graves' disease), and nodular or adenomatous goiter. It will be noticed that the first type is named from a microscopic feature, the second from a leading symptom (which may be absent), and the third from the

gross appearance. This is hardly a satisfying or scientific basis, but it is the best we have. The clinicians speak of diffuse non-toxic and toxic goiter and adenomatous non-toxic and toxic goiter. This is quite justifiable, but the pathologist is unable to relate these terms to morphological changes in the thyroid. The terms toxic and thyrotoxicosis indicate a clinical picture similar to that produced by over-dosage with thyroid extract. Whether or not the three main forms of goiter are separate entities is a matter of dispute. While it is true that extreme examples differ enormously from one another, yet intermediate types will be found to bridge the gaps, clinical as well as pathological. In spite of this it is possible that different etiological agents are operative in the different forms.

The *geographic pathology* of goiter varies greatly (Hellwig). This serves to explain the conflicting accounts which are found in the writings of observers in different parts of the world. The goiter of North America, for instance, is very different from that of the Himalayas and the Alpine districts of Switzerland. In the former the common variety is the diffuse and nodular colloid goiter with large acini distended with colloid (macrofollicular type), whilst in the latter parenchymatous goiter is the usual form characterized by small follicles poor or lacking in colloid (microfollicular type). Thyrotoxic symptoms are commoner in North America than in any other country. Thus in Berne, Switzerland, 3 per cent of goiters are associated with thyrotoxicosis, whereas in Portland, Oregon, 67 per cent fall in the toxic group. In mountainous countries the microfollicular non-toxic type is prevalent; in level countries the macrofollicular, often associated with toxic symptoms, is common.

### DIFFUSE COLLOID GOITER

This type of goiter includes those varieties known as simple goiter, endemic goiter and adolescent goiter, although these various terms are by no means synonymous. It is the most physiological form of thyroid disease, for it commences as a compensatory or work hypertrophy, but physiological limits in the thyroid are easily transgressed, and when the gland has met the demand of the tissues it may be unable to return to its former size.

The main *causal factor* in endemic goiter is an insufficient supply of iodine to the thyroid, which in consequence develops a work hypertrophy followed later by involution. The soil of high countries is denuded of iodine, so that the drinking water is poor in that element. In the endemic region of North America, particularly the region of the Great Lakes and the valley of the St. Lawrence, the soil is iodine-poor, having been deposited from the melting of the ice of the last glacial epoch. Animals as well as men living in endemic regions suffer from simple goiter. This type of goiter is a deficiency disease due to lack of iodine. McCarrison believes that bacterial infection of water plays an important part in pathogenesis. The bacteria may absorb



the iodine before it can be taken up by the thyroid and produce simple goiter in this way rather than by a direct toxic action on the gland.

It is not suggested that all simple goiter is caused by a lack of iodine in the water and food, for it would be difficult to explain the sporadic cases on this basis. Infections and intoxications may play a part by deviating the iodine from the thyroid or by increasing the need of the body for thyroxin. A high fat diet, as McCarrison has shown, may quickly exhaust the iodine store of the thyroid. But it will be noticed that though we start out by devious routes, we always return in the end to the question of iodine shortage.

Simple colloid goiter is much commoner in women than in men. It commonly appears in girls at the time of puberty or soon after. It tends to disappear after a few years, so that the usual age period is from fifteen to twenty-five years. In endemic regions the condition tends to appear earlier and last longer. It may be due to a relative rather than an absolute lack of iodine. There may be enough iodine in the food and water for ordinary purposes, but not for the increased demand for thyroxin at adolescence and puberty. Similar enlargement may occur during pregnancy and lactation and for a similar reason. Such goiter responds remarkably to the administration of iodine when in the hyperplastic stage.

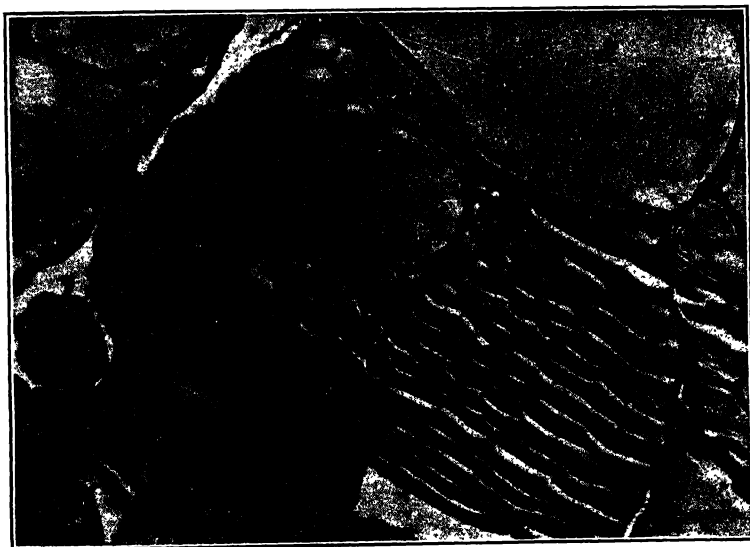


FIG. 382.—Colloid goiter. The acini vary much in size, some being widely dilated. The colloid is abundant and stains deeply. The epithelium is flattened.  $\times 75$ .

**Lesions.**—It is very seldom that one has the opportunity to study the goiter of adolescence during the hyperplastic stage, for it should never be removed surgically. When the gland is removed in the involutionary or colloid stage, as may have to be done on account of

its increasing size, it is found to be uniformly and diffusely enlarged and of soft consistence. The cut surface is amber in color, and presents a finely honey-combed translucent appearance, owing to the distended acini being filled with colloid.

The *microscopic appearance* may resemble that of normal thyroid tissue, but there is greater irregularity. Many acini are greatly enlarged. Some are of normal size and some are smaller than normal. All are filled with densely stained colloid of a high iodine content. (Fig. 382.) The epithelium is low, and in the larger acini it may be flattened. A few small islands of hyperplasia may still be present, and evidence of former hyperplasia is apparent in the form of withered spurs which still project here and there from the acinar walls. The vascularity is not increased. The stroma may be increased in places, and fibrous bands may intersect the gland, accentuating the normal tendency which the thyroid shows toward lobulation.

In North America the term simple goiter is synonymous with diffuse colloid goiter. In the great endemic mountain regions of the Alps and the Himalayas it is parenchymatous goiter. This is diffuse enlargement of the thyroid marked by great numbers of small closely packed acini lined by cubical epithelium and lacking in colloid. This is similar to the so-called fetal adenoma of North America.

### NODULAR OR ADENOMATOUS GOITER

As the years pass a goiter tends to become nodular. The nodular formations are commonly known as adenomas. The term is unfortunate, because in the majority of cases these tumors are not true neoplasms, but it is in such common use that it will be employed here. In man (as opposed to the lower animals) hyperplastic changes tend to be rather patchy, so that areas become localized which are demarcated still further by the fibrous septa of the gland and eventually they may become encapsulated like true tumors. During the hyperplastic stage the general swelling of the gland obscures the nodules, but when this subsides as the result of involution the nodules become apparent. They may not be detected clinically, but the cut surface shows them up at once. The number increases rapidly with age, so it is natural that a nodular thyroid causing toxic symptoms (so-called toxic adenoma) should occur at a later age than a diffuse toxic goiter (Graves' disease). Two types of lesion occur, called colloid adenoma and fetal adenoma. There is difference of opinion as to whether these should be regarded as different entities. The arguments for and against may be read in Joll's admirable monograph.

**Colloid Adenoma**, or more properly colloid nodular goiter, is the commonest type of goiter demanding surgical treatment in North America. The nodule may be single, but more often it is multiple. (Fig. 383.) Large numbers of small nodules may be scattered through a diffusely enlarged gland, a condition known as adenomatosis. More often one or more nodules enlarge and deform the outline of the gland,

so that lumps can be detected clinically. The larger nodules are well encapsulated by fibrous tissue. The cut surface is identical in appearance with the surrounding gland; this is natural, as it is merely a part which happens to be separated off by fibrous septa. *Degenerative changes*, such as softening, cyst formation, and hemorrhage are of common occurrence. When a thyroid nodule suddenly enlarges it is most probably due to hemorrhage into a cyst. The fluid in the cyst may be clear and shimmering with cholesterol crystals, but often it is colored brown by old blood. Calcification is quite common in the center of the adenoma or in the wall of a cyst. The *microscopic appearance* is the same as that of the surrounding gland, except that it is surrounded by a fibrous capsule. The acini just outside the capsule may be greatly narrowed as the result of pressure. The adenoma may or may not show hyperplastic changes, depending on whether the rest of the gland happens to show these changes. Sometimes the hyperplasia is more marked in the adenoma, which seems to become a center of greater activity.



FIG. 383.—Nodular goiter. The large nodules are of the colloid type, while the small nodules at the bottom left-hand corner are of the fetal type.

**Fetal Adenoma** is a name dependent on a disproved theory that the lesion arose from fetal cell rests. It is commoner in young people, often beginning about the time of puberty and being distinguishable as a firm nodule in the midst of the soft goiter of adolescence. Unlike the rest of that goiter, it does not respond to treatment with Lugol's solution. The tumor is usually solitary, and is often the only thyroid lesion. It pushes the gland aside in a way which is not seen in the case of colloid nodules, and is surrounded by a heavy fibrous capsule. The cut surface is dense and elastic, of an opaque pink or gray color, often streaked with yellow areas of necrosis, and frequently presenting a white fibrous somewhat stellate core near the center. For these reasons it has been thought by some, perhaps with justice, that the lesion is

a true tumor of the thyroid, and therefore entirely different from colloid nodules. Degenerative changes, cystic, hemorrhagic and calcareous,

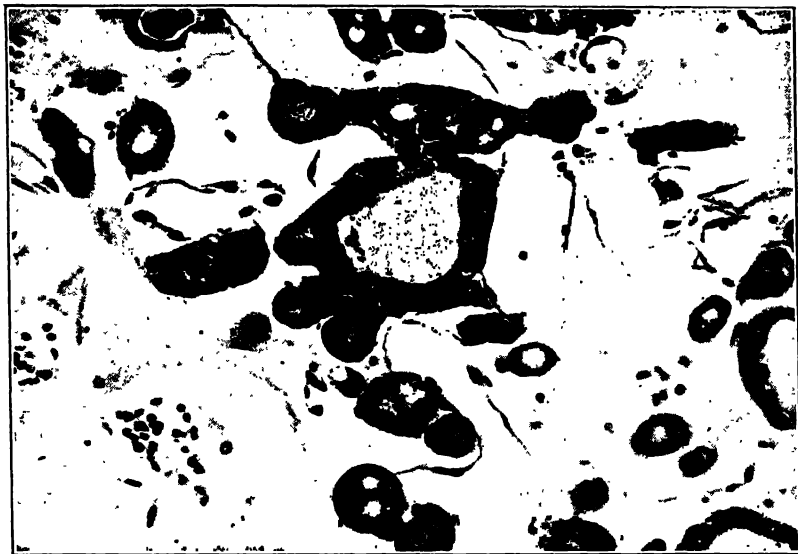


FIG. 384.—Adenoma of the thyroid. The acini are very small and are widely separated by a structureless material. The vessels are markedly dilated. There is apparent budding of the acinar epithelium, with formation of new acini.  $\times 250$ .

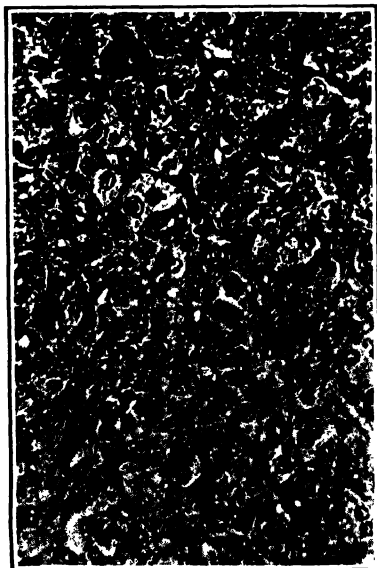


FIG. 385.—Adenoma of thyroid; solid collections of acini.  $\times 275$ .

are even more frequent than in the colloid nodules, and the tumor may be replaced by a cyst with a calcified wall.

The *microscopic picture* is strikingly different from that of the colloid nodules, unless degeneration has blurred the outlines. The tumor consists of small acini which contain little or no colloid. This is the picture of the microfollicular parenchymatous goiter so common in the endemic regions of Europe, although it is a diffuse, not a localized lesion. The colloid increases in the older specimens until finally the appearance may resemble that of a colloid nodule. The alveoli are often widely separated by a structureless hyaline stroma which has a mucoid or edematous appearance, and contains numerous, large, thin-

walled vessels from which hemorrhage can readily occur. Some of the acini may show an appearance of epithelial budding with the formation of new acini. (Fig. 384.) Sometimes the tumor consists of solid masses or trabeculae of cells without any attempt at acinar formation (Fig. 385); such lesions strongly suggest a true tumor.

### EXOPHTHALMIC GOITER—GRAVES' DISEASE

Graves' disease is an enigma and constitutes one of the most perplexing problems in the whole of medicine, for it provides an example of an organ starting and continuing to hyperfunction without any regard to the needs of the body. It bears no apparent relation to iodine deficiency. There is often a very definite history of nervous or psychic shock, not infrequently sexual in character. In some cases the onset of the disease has followed such a shock within a few days. The tendency at present is to look beyond the thyroid in seeking the essential cause of Graves' disease. The pituitary is a possibility, since the thyrotropic hormone of that gland is the most powerful stimulator of thyroid hyperplasia. As there is excitement of the sympathetic system the adrenals may play a part. Most persons who develop Graves' disease belong to a certain type, the so-called Graves' constitution. They are of slender build, temperamental, easily overstimulated, with rapid pulse and slight tremors, and especially sensitive to the administration of thyroid extract. It would appear that in such persons something serves to upset the normal balance which should exist between the ductless glands (pituitary, adrenals, thyroid), one result of which is overstimulation of the thyroid, and that this balance may never be permanently regained.

**Symptoms.**—The disease is much commoner in women than in men in the proportion of 5 to 1. It usually begins in early adult life and the onset is often sudden and acute. When it develops in later years the onset is more gradual. The symptoms of Graves' disease are due to excitation of the sympathetic system. The four cardinal signs are enlargement of the thyroid, exophthalmos, tachycardia, and tremors. The skin is moist and liable to vasomotor disorders such as flushing; the patient is excitable; palpitation, diarrhea, and vomiting may occur; there is loss of weight and an enormously increased body metabolism as indicated by calorimetric observations. The course of the disease varies. It may be acute and fulminating, the patient dying with all the classical symptoms of exophthalmic goiter; sometimes he dies in a so-called thyroid storm after thyroidectomy. In other cases the course is less violent, and is marked by a series of remissions and exacerbations. Gradually the fire burns itself out, the thyroid breaks down under the constant stimulation, and a condition of partial thyroid insufficiency (myxedema) may develop. There is profound disturbance in iodine metabolism, as indicated by raised blood iodine, increased excretion of iodine, and a negative iodine balance. This increased mobilization of iodine in hyperthyroidism resembles the disturbed calcium metabolism of hyperparathyroidism.

**Lesions.**—The thyroid gland is moderately or considerably enlarged, but the largest goiters do not occur in Graves' disease but in the adenomatous and colloid forms. It must be remembered that no

enlargement may be detected clinically, as the hypertrophied lobes may be behind the trachea. The gland, over which greatly dilated veins may course, is firm, pink in color owing to the increased vascularity, and of a dense meaty appearance which is in marked contrast to the translucency of the normal thyroid. If the patient has been given iodine (Lugol's solution) before the thyroid gland was removed, the characteristically dense appearance is lost owing to the temporary change from a hyperplastic to a colloid condition. The enlargement is diffuse, but the cut surface shows a fine lobulation which, together with the meaty appearance, suggests a resemblance to the cut surface of the pancreas.

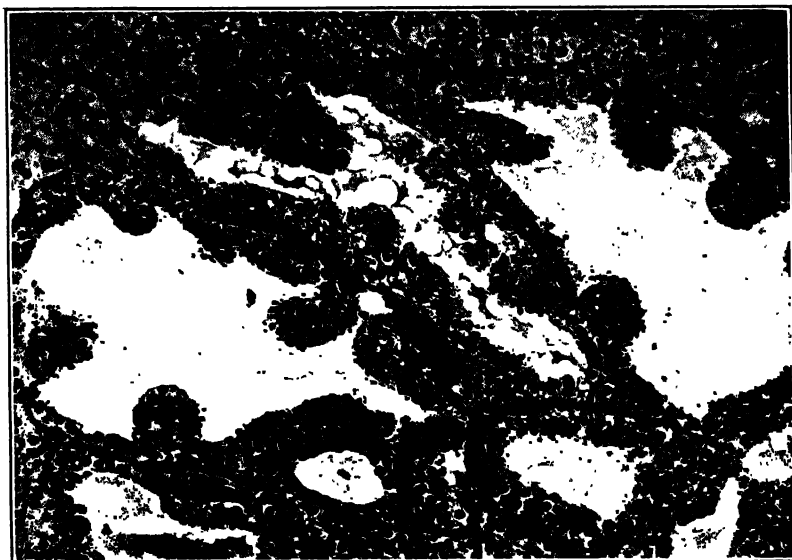


FIG. 386. —Thyroid of Graves' disease undergoing involution under iodine treatment. The papillary processes are being withdrawn from the enlarged acini, and the colloid is reappearing. Above and below there is still dense hyperplastic tissue.  $\times 150$ .

The *microscopic picture* shows three characteristic changes: epithelial hypertrophy and hyperplasia, disappearance of colloid, and lymphoid hyperplasia. The epithelium is tall and columnar, and mitotic figures may be numerous. The acini are greatly enlarged and very irregular, but this enlargement is not readily obvious unless a wax reconstruction is made, for they are filled with the papillary processes which form in order to accommodate the new formation of cells. (Fig. 386.) Sometimes there is no enlargement of acini with infolding of their walls, but a formation of great numbers of small rounded acini lined by columnar epithelium. In both forms the colloid is thin and scanty or has completely disappeared. The change in the colloid is most marked where it comes in contact with the lining epithelium, as

if it is being absorbed by the acutely active cells. Scattered throughout the stroma are lymphoid follicles with definite germinal centers (Fig. 387), in addition to which there may be a more diffuse infiltration with lymphocytes. The lymph follicles become larger and more distinct after prolonged treatment with Lugol's solution. It is probable that they are a result of the hyperplasia and hypersecretion of the thyroid. Wegelin points out that the lymphoid tissue in the thyroid appears to be developed as a purely local response to irritation and not as part of a thymico-lymphatic constitution. There is a marked increase in the vascularity in keeping with the general increase in glandular activity.

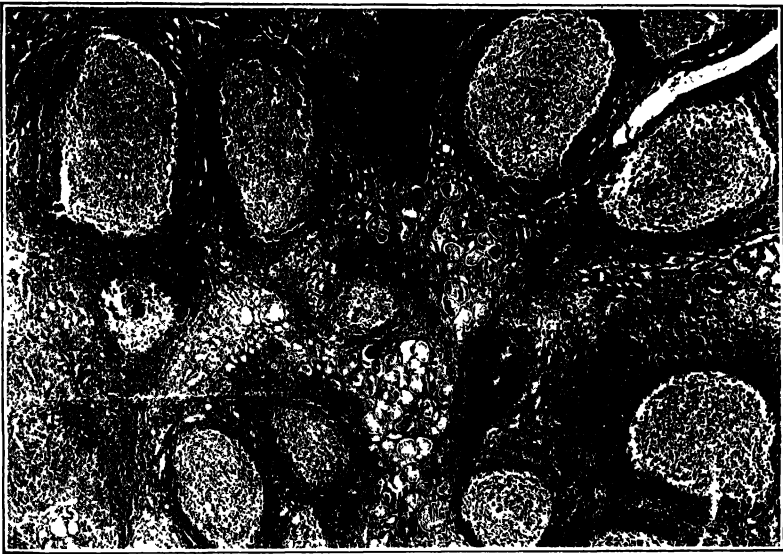


FIG. 387.—Hyperplastic thyroid showing an extreme degree of lymphoid hyperplasia. The patient had been treated with Lugol's solution.  $\times 40$ .

When the patient has had a short preoperative course of Lugol's solution the picture is markedly changed, corresponding with the great abatement in the symptoms of thyrotoxicosis. The epithelial hypertrophy and hyperplasia subside, colloid reappears, and the lymphoid tissue is less abundant. But when the administration of iodine is prolonged for weeks or months a different picture develops, which bears a spurious resemblance to the resting colloid gland. Epithelial hypertrophy is still absent and the atrophic looking follicles are lined by a low type of cell, but the colloid is thin and watery, lymphoid hyperplasia is very marked, the germinal centers of the follicles are remarkably large and pale, a condition which Warthin calls lymphoid exhaustion, and there is proliferation of the stroma. The symptoms meanwhile may have returned in full force.

Thiouracil, a derivative of thiourea, produces a curiously contrasted effect. The clinical symptoms of hyperthyroidism are relieved and the basal metabolic rate lowered, but the resorptive phase of thyroid physiology appears to be intensified, for the colloid is diminished in quantity and density and may finally disappear, whilst the epithelium is tall and columnar. Thiouracil thus appears to inhibit the production of new colloid, but does not interfere with the use of the available colloid (Halpert).

*Lesions in other organs* deserve at least passing mention. The hyperplasia of the *thymus* and *lymphoid tissue* has already been mentioned. A persistent and enlarged thymus is found at autopsy in the majority of cases of typical exophthalmic goiter. The lymph nodes, tonsils, Peyer's patches, and lymphoid follicles in the spleen may all show hypertrophy similar to that of status lymphaticus. In some of my fatal cases there has been tremendous lymphoid hyperplasia of the appendix, the lymphocytes obliterating the mucosa and lumen, and infiltrating the muscular wall. The *blood* shows a relative lymphocytosis. The heart is often enlarged, and may show myocardial degeneration and fibrosis, but there are no specific lesions. The *muscles* show fatty degeneration; in the quadriceps extensor this accounts for the difficulty the patient has in lifting his foot to a height (quadriceps sign). The *adrenals* may be atrophic, but there are no specific lesions. The *liver* often shows passive congestion, and degenerative lesions are common. Fatty change is extremely frequent. There may be acute necrosis, both focal and central. Or there may be subacute toxic atrophy, with the development of cirrhosis and nodule formation. Liver function tests often show a marked degree of impairment. It has been suggested by Boyce that in thyrotoxicosis the overstimulated metabolism results in combustion of the protective glycogen of the liver beyond the degree of safety. When that point is reached there develops sudden and extreme hyperpyrexia, an almost uncountable pulse, vomiting, diarrhea, and restlessness which may pass into delirium coma and death. This picture is known as thyroid crisis or thyroid storm. The *bones* often show marked rarefaction and decalcification due to a lacunar absorption brought about by osteoclasts and associated with a great excretion of calcium.

**The Relation of Symptoms to the Lesions of Goiter.**—*Diffuse colloid goiter* usually produces no symptoms, except possibly those of pressure. On the other hand there may be mild degrees of thyrotoxicosis or of hypothyroidism. Microscopic examination of the thyroid fails to give a satisfactory explanation of these differences. The parenchymatous, microfollicular, colloid-poor goiter so prevalent in the mountainous regions of Europe is hardly ever associated with toxic symptoms.

In *Graves' disease* the cardiovascular phenomena and the increased basal metabolic rate are manifestations of hyperthyroidism, which itself is presumably caused by epithelial hyperplasia. But there are difficulties. A patient may have well marked symptoms of hyperthyroidism without epithelial hyperplasia, especially when iodine treatment has been too prolonged. Goiter in adolescents in regions of severe goiter may show all the microscopic changes characteristic of Graves' disease, yet thyroid function may be normal. The administration of thyroxin does not produce the exophthalmos and other neurological phenomena of Graves' disease. Indeed exophthalmos may get worse after removal of the thyroid; so-called malignant exophthalmos developing after operation may destroy the eyeball. There is no agreed explanation for the exophthalmos, but in severe cases the extraocular muscles and orbital connective tissue may be greatly swollen owing to edema. Exophthalmos associated with orbital edema can be produced experimentally by injection of the thyrotropic hormone of the anterior pituitary, even though the thyroid has first been removed. This is due to a mucoid type of edema of the orbital



fat, which is particularly rich in loose connective tissue and is therefore readily infiltrated. It seems probable that the stimulus responsible for the exophthalmos is the thyrotropic hormone of the pituitary acting through the cervical sympathetic on the orbital tissues. Thyroidectomy removes the inhibitory effect of the thyroid on the pituitary, thus explaining the occasional post-operative intensification of the exophthalmos. It has been suggested that in Graves' disease the thyroid allows thyroxin to leak from the gland (thyroid diarrhea), and that the hyperplasia is an attempt to compensate for the rapid loss of hormone, and therefore merely a secondary phenomenon. This sounds well, but it may have more sound than meaning.

The chief symptom of *adenomatous goiter* is local pressure on the trachea, which may cause marked narrowing of that structure with dyspnea. Hemorrhage into an adenomatous cyst may aggravate the condition in a sudden and alarming manner. A *retrosternal goiter*, usually due to the downward extension of an adenoma, is a cause of dyspnea which may escape detection for some time. The presence of an adenoma may or may not be associated with signs of hyperthyroidism. On this account the clinician distinguishes between two forms of adenoma, the toxic and the non-toxic. This may be convenient clinically, but there is no pathological justification for the distinction, for it is quite impossible to tell microscopically if an adenoma is toxic or not. It is not the adenoma but the entire gland which is responsible for any symptoms of hyperthyroidism that may happen to be present.

Nor has the distinction between exophthalmic goiter and toxic adenoma any sound pathological basis. They are both varieties of Graves' disease, the former acute, the latter chronic and characterized by a predominance of cardiovascular symptoms and an absence of exophthalmos. It is a difference of degree rather than of kind. English writers speak of *primary* and *secondary Graves' disease*. The primary form is the ordinary classical type in which toxic symptoms are present from the beginning, whereas in the secondary form the thyroid has been enlarged some years before the toxic symptoms develop, and the gland is usually nodular. The toxic adenoma appears later in life than exophthalmic goiter, at a period when there is less thyroid epithelium which is capable of reacting violently to the stimulus, so that exophthalmos is absent and the nervous symptoms are less marked. On the other hand, the myocardium is more easily exhausted and fibrillation is readily produced. In the chronic form it is natural that adenomata should make their appearance, but they are not responsible for the symptoms of thyrotoxicosis, for they merely represent an incident in the course of the pathological process. If the adenoma is very large and contains much hyperplastic tissue, its removal will be followed by improvement, but this fact does not invalidate what has just been said. As a matter of fact the term toxic adenoma in the hands of the clinicians has come to mean hyperthyroidism without eye symptoms rather than the presence of an adenoma.

## CRETINISM AND MYXEDEMA

Deficiency of the thyroid secretion gives rise to very characteristic symptoms and may be caused in a variety of ways. The basis of the condition may be congenital or acquired. The former is known as cretinism, the latter as myxedema.

**Cretinism.**—If the thyroid does not develop properly during fetal life, or if it is acted on during that period by goitrogenous influences, the child is born a cretin. Cretinism may be endemic or sporadic. The *endemic* form is common in the great regions of endemic goiter, the Alps and the Himalayas. It has been said that goiter is the first step on the road to cretinism. The mother almost always suffers from simple (endemic) goiter. The child at birth has not got a goiter, but

in a few years he usually develops one unless removed to a non-goitrous district. At first the thyroid may show a compensatory hyperplasia, but later there is exhaustion atrophy although the gland is still enlarged. Endemic cretinism can be prevented by giving the pregnant woman a sufficient amount of iodine. The *sporadic* form occurs in non-endemic regions. The cause is not known, but is apparently something that interferes with the development of the thyroid, which is represented by a fibrous remnant. Indeed it may be difficult to find any trace of thyroid tissue, so that goiter does not develop.

The cretin is a dwarf physically and mentally. The mind, the skeleton, and the sexual organs do not develop. Like Peter Pan, the cretin never grows up, but he has none of Peter's vivacity, for the vitalizing influence of the thyroid is lacking. He is a sad, old child. The stature is stunted, the head large, the face broad, the features coarse, the arms short and curved, the sexual organs undeveloped, and the mental powers little better than those of an imbecile. What was intended to be created in the image of God has become what has been called the pariah of Nature, and all for want of a little iodine!

**Myxedema.**—This is the condition of thyroid deficiency in the adult, and usually appears about the age of forty years. It is commoner in women. It has no relation to goiter, and is not commoner in the regions of endemic goiter. It may be due to some extrathyroid cause, such as pituitary deficiency. Some cases of Simmonds' disease (pituitary insufficiency) may simulate myxedema, for in that condition there is atrophy of the thyroid; this has been called the pituitary type of myxedema (Means). Usually, however, there is no clinical evidence of pituitary disease in myxedema, nor any significant histological changes in the pituitary. The thyroid gland is atrophic, hard, and in the most severe cases is converted into a mass of fibrous tissue. As a rule areas of atrophic glandular tissue remain separated by an abundant fibrous stroma. Lymphoid collections are frequent, and are probably related to the disappearing parenchyma as in chronic nephritis. (Fig. 388.)

The *clinical picture* in an advanced case is so characteristic that the diagnosis can be made at a glance, but owing to the efficacy of treatment with thyroid extract such cases are seldom seen nowadays. The woman is heavy and intensely phlegmatic, the face broad and devoid of all expression, the skin rough, dry, and singularly sensitive to cold. Persons with hyperthyroidism have a moist skin and rarely feel the cold, those with hypothyroidism have a dry skin and continually feel cold because the metabolic fire is burning so low. The hair is dry and falls out, often beginning first in the outer third of the eyebrows. The basal metabolic rate is characteristically low. The serum cholesterol is invariably high in untreated cases and decreases on treatment. Its estimation is therefore of great value in the diagnosis of myxedema, and it is a better indicator than the basal metabolic rate, as it is less dependent on the coöperation of the patient. It must be remembered that cases encountered in practice are not likely to

show this full-blown picture, and have to be recognized when the symptoms are much less marked.

The disease owes its name to a solid pseudoedema of the skin and mucous membranes caused by infiltration with a mucin-like substance, so that the tissue appears to be myxomatous. It is this infiltration which serves to iron out the expressive wrinkles and folds of the face, so that all the patients have a strong family resemblance to one another. The change is most marked in the face, neck, supraclavicular fossæ, and the backs of the hands, which are fat and clumsy. The mucous membranes are also infiltrated, so that the tongue is thick, and there is swelling of the mucous membrane in the nose, mouth, larynx, bronchi, and alimentary canal. A similar change in the heart may cause great

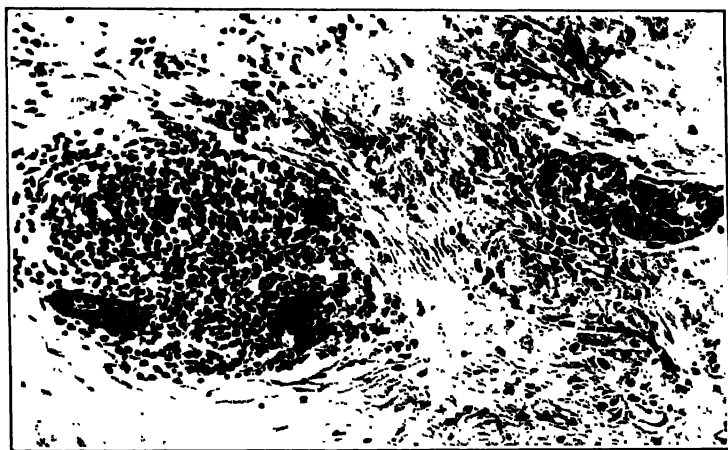


FIG. 388.—The thyroid in myxedema. The glandular tissue has been replaced by fibrous tissue; remnants of acinar epithelium remain surrounded by lymphocytes.  $\times 125$ .

enlargement (myxedema heart). The edema, which may be associated with serous effusion in the pericardial cavity, may be dependent on a change in the capillary permeability, which can be shown experimentally to be markedly increased in myxedema (Lange). With thyroid therapy the permeability rapidly returns to normal. Cardiac edema is not associated with increased capillary permeability. There is advanced atrophy of the interstitial cells of the testis, accounting for such gonadal symptoms as impotency and loss of desire (Marine).

*Cachexia strumipriva* is postoperative myxedema caused by too radical removal of a goiter (struma). The condition, which is characterized by marked wasting as well as the ordinary symptoms of myxedema, was common in the early days of goiter surgery, but is very rarely seen at the present time.

## TUMORS OF THE THYROID GLAND

**Carcinoma.**—Carcinoma commonly arises in a preëxisting adenoma, usually of the fetal type. It is not possible to give the precise percent-

age of this occurrence, because the tumor so often has overgrown the original site. The adenoma may be quite small, it is generally non-toxic, and the malignant change may occur in youth or even in childhood. Carcinoma is commoner in women than in men, because of the much higher incidence of nodular goiter in the female. Wegelin points out that in Berlin where the incidence of goiter is low there were 13 malignant tumors of the thyroid in 13,426 autopsies, whereas in Berne where the incidence of goiter is high there were 159 malignant tumors in 15,250 autopsies. It bears no relation to Graves' disease. This is strange, because in that disease there is a wilder epithelial proliferation than in any other non-neoplastic lesion. The tumor is hard and



FIG. 389. Carcinoma of thyroid, medullary form. Sheets of cells surround acini containing colloid.  $\times 375$ .



FIG. 390.—Carcinoma of the thyroid. Papillary processes project into large spaces. There is no colloid.  $\times 175$ .

rapidly growing, causing pressure on the trachea with dyspnea. There is pain and fixation to the surrounding parts. All of these features are present in Riedel's struma (see p. 778). The tumor at first shares the capsule of the adenoma, but later infiltrates the surrounding gland and invades the regional lymph nodes. Long before this happens distant metastases may have been set up by early invasion of the bloodvessels. Carcinoma may sometimes cause symptoms of hyperthyroidism.

The *microscopic picture* varies greatly and many different names have been applied, but it is sufficient to recognize adenocarcinomatous, medullary (Fig. 389), and scirrhus forms. The last is quite rare. The

adenocarcinomas often take a papilliferous form, with the formation of papillary processes in the glandular spaces. (Fig. 390.) I have seen a tumor closely mimic a hypernephroma, and these hypernephroid tumors have been described by other writers. Different parts of the tumor may vary considerably in structure, and in places the picture may be practically that of the normal or slightly hyperplastic thyroid. Invasion of the veins occurs early and accounts for the early occurrence of distant metastases. The presence of tumor cells within the lumen of a vein is of great diagnostic value in cases where the microscopic appearance is atypical (Graham). The distinction between benign and malignant hyperplasia is sometimes very difficult.

*Metastases* may occur early, owing to the marked tendency which the tumor shows to invade the blood-vessels. The lungs and the bones are the common sites of secondary growths. The condition known as "benign metastasizing goiter" was for years described in the textbooks; it is characterized by the occurrence of a bone tumor composed of more or less normal thyroid tissue in association with what was supposed to be a colloid goiter. All of these cases are really examples of carcinoma, and definite evidence of malignant disease of the thyroid will appear in due time.

#### Lateral Aberrant Thyroid Tumors.--

These not uncommon tumors form a very distinct pathological and clinical entity. The tumor, usually in a young person, is situated in the anterior triangle of the neck. It is well circumscribed and of slow growth, but tends to extend to the regional lymph nodes, in this respect differing from ordinary carcinoma of the thyroid which spreads by the blood stream. *Microscopically* its chief characteristic is its adenomatous and often cystic form and the presence of papillary processes. It is a papillary cystadenoma, and it may be very difficult to determine if the lesion is a benign or malignant one. If the latter, it is of low grade, but there is a tendency to recurrence after removal. Perhaps this statement is not accurate, for the apparent recurrence may really be an indication of fresh centers of growth. In the development of the thyroid there is a migration of epithelial cells derived from a posterior pharyngeal outpouching which should fuse with the median thyroid anlage in its descent. If this fails to occur these cells form the lateral aberrant thyroids, which may give rise to adenomatous tumors of papillary type with cyst formation and a tendency to malignant change. Clinically the lesion is often mistaken for lymph node tuberculosis, Hodgkin's disease, etc.



FIG. 391.—Hürthle-cell adenoma.  
× 240.

**Sarcoma.**—Sarcomas of the thyroid gland are often described, but most if not all of these are really examples of anaplastic carcinoma. The cells may be spindle-shaped and arranged quite diffusely, but careful search will reveal places where the arrangement is epithelial in character with attempted formation of acini.

**Hürthle-cell Tumor.**—This is an adenoma the cells of which bear a striking resemblance to those of the liver, for they are large, polyhedral, with abundant strongly acidophilic cytoplasm, and arranged in trabeculae or small acini. (Fig. 391.) The lesion is usually benign, but may be malignant (adenocarcinoma); in the latter case the cells show the usual malignant characteristics. In 1894 Hürthle described a large acidophilic cell on the outer surface of the wall of the follicles, and the tumor is supposed to arise from these cells, but it is more probable that the acidophilic character of the cells signifies a functional change such as often occurs in the normal thyroid, and that they are not separate anatomical structures. The term *Langhans' tumor* (wuchernde struma) occurs frequently in European literature. It is difficult to be certain of the identity of this lesion, but it seems to bear a close resemblance to the Hürthle-cell tumor, although usually markedly invasive.

**Secondary Tumors.**—Secondary tumors of the thyroid are rare, with the exception of melanoma and carcinoma of the lung.

### INFLAMMATION OF THE THYROID GLAND

The thyroid gland is singularly immune from acute inflammatory lesions. A mild form of thyroiditis may be present in acute tonsillitis, acute articular rheumatism, typhoid fever, and less frequently in other infections. *Suppuration* is rare. When it does occur the gland is hot and swollen, and an abscess forms which may discharge into the larynx, trachea, or esophagus.

**Riedel's Struma.**—This is a form of chronic thyroiditis. The gland enlarges rather quickly and uniformly, although only one lobe may be involved, it is of a whitish color, and merges with the surrounding tissues to which it is very firmly adherent. Its most striking characteristic is its extraordinary hardness, which is described in such names as "iron-hard tumor" and "woody thyroiditis." Microscopically there is at first a marked infiltration with lymphocytes. These are replaced later by a very dense sclerotic tissue. (Fig. 392.) DeCoursey suggests that the starting point of the disease may be a perithyroiditis, which causes partial constriction of the vessels entering the thyroid gland, and that the fibrosis begins outside rather than within the gland. There is marked degeneration and destruction of the glandular tissue. The epithelial cells may fuse around small masses of colloid so as to produce an appearance like that of a giant cell, and the condition is easily mistaken for tuberculosis. There may be large numbers of these pseudogiant cells. In other cases areas of irregular cellular hyperplasia may closely simulate carcinoma. The lesion may progress so that the patient passes into a condition of myxedema, but it is remarkable how much destruction of tissue there may be with no symptoms of hypothyroidism. The progress of the disease may be arrested at any time, and great benefit may be produced by even partial resection, which appears to relieve the pressure on the rest of the gland.

**Hashimoto's Struma.**—The best name for this condition is *lymphadenoid goiter*, but it is usually called Hashimoto's struma or Hashimoto's disease. The lesion is almost confined to women over middle age in contrast to Riedel's struma which may occur in men. The thyroid is enlarged and of a uniform pale gray color with complete loss of the normal colloid appearance, firm in consistence, but without the woody or iron-hard character of Riedel's struma, nor is it adherent to the surrounding structures. There is a much greater tendency to myxedema. Microscopically the acini are replaced by a dense infiltration of lymphocytes, amongst which germinal centers may be found. (Fig. 393.)



FIG. 392.—Riedel's struma.  $\times 120$ .

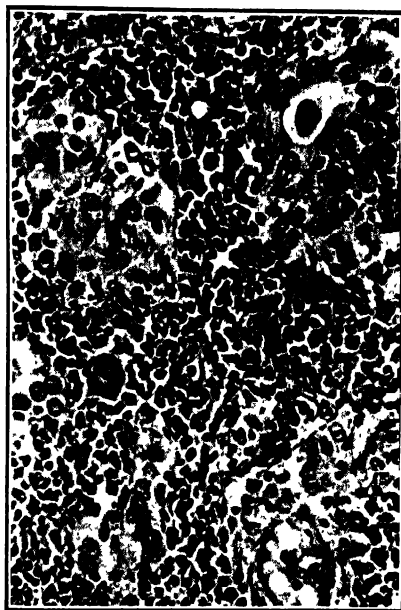


FIG. 393.—Hashimoto's struma, showing diffuse infiltration with lymphocytes.  $\times 250$ .

There is difference of opinion as to whether Hashimoto's struma and Riedel's struma are two different diseases, or whether the latter is merely the terminal fibrosed stage of the former. A typical picture of lymphadenoid goiter is certainly very different from the scarred thyroid of Riedel's struma, but when one studies a series of cases it becomes very difficult to know in which group to put some of the specimens. I have observed one case of Hashimoto's disease at autopsy in which the microscopic picture differed little from that of the surgical specimen removed seven years previously. Similar cases have been reported (Helligwig). This and the other considerations already mentioned tend to support the view that the two conditions are unrelated.

## OTHER LESIONS OF THE THYROID GLAND

**Infective Granulomas.**—*Tuberculosis* of the thyroid gland is rare, the gland showing a remarkable resistance to this infection. Miliary tubercles may occur, but must be distinguished from the pseudotubercles of Riedel's struma, and from similar structures which are very occasionally seen in diffuse and nodular goiters. Large areas of caseation may be formed, but this is extremely rare. *Syphilis* may not uncommonly cause enlargement of the thyroid in the secondary stage. Tertiary gummata are very rare.

**Congenital Anomalies.**—The thyroid may be absent. Normally the gland is developed as a downgrowth from the anterior wall of the pharynx, the stalk connecting it with the pharynx forming the *thyroglossal duct*, which at birth is represented only by the dimple of the foramen cecum at the posterior part of the tongue. Portions may be displaced during the course of development. A nodule at the base of the tongue may form a *lingual thyroid*. There may be small masses in the neck known as *accessory thyroids*, and pieces may be found at some distance from the normal position. A portion of the duct may remain unobliterated and form a *thyroglossal cyst*, which is recognized by always being in the middle line of the neck. Pieces of parathyroid or thymus may be embedded in the thyroid.

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## THE PARATHYROID GLANDS

**Pathological Physiology.**—The parathyroid glands regulate the level of the blood calcium; they determine the rate of movement from the great calcium depots, the bones, into the blood stream and tissues, and from thence out into the urine. The blood phosphorus tends to vary inversely with the blood calcium; as the one goes up the other goes down. Renal disease may cause retention of inorganic phosphorus; this tends to depress the calcium, and would do so were it not for increased function of the parathyroids and consequent hyperplasia. Just as renal lesions can influence the parathyroids, so also can parathyroid overactivity cause renal lesions. Thus Chown and his associates found that animals injected repeatedly with parathyroid extract had marked deposition of calcium in the renal tubules causing obstruction with atrophy of some nephrons and dilatation of others. The amount of calcium in the tissues determines their neuromuscular irritability, the irritability varying inversely with the amount of calcium. The pathological physiology of the gland may vary in the direction of hyperfunction or hypofunction. Pure hyperparathyroidism gives rise to generalized osteitis fibrosa, pure hypoparathyroidism gives rise to tetany.

The parathyroids are the most difficult organs in the body to find at autopsy, partly on account of their small size, partly because of their resemblance to lobules of fat. Excellent instructions for their demonstration will be found in the appendix to Gilmour's paper.

**Hyperparathyroidism.**—In 1925 Collip succeeded in preparing a powerful extract of the active principle of the parathyroids (parathormone). Its action is to remove calcium from the bones in large amount, and owing to this mobilization of calcium the bones become rarefied, the blood calcium rises, and there is a marked excretion of calcium and phosphorus in the urine. The decalcification of bone is followed by the formation of fibrous bone lesions. The muscles are hypotonic, for the tissues are flooded with the mobilized calcium, and the neuromuscular irritability is accordingly diminished. The pathological counterpart of experimental hyperparathyroidism is *generalized osteitis fibrosa cystica*, which is usually associated with tumor of the parathyroids. Multiple bone cysts may be formed. There is hypercalcaemia and an increased excretion of calcium in the urine. As the phosphorus of the blood usually varies inversely with the calcium, it is low in this condition.

There is a relationship between the parathyroid and kidneys as well as between the parathyroid and bones. Moreover this relationship is a reciprocal one. Hyperparathyroidism causes metastatic calcification of renal tubules which may lead to renal insufficiency. Conversely, prolonged renal insufficiency due to chronic glomerulonephritis, etc., is often associated with marked secondary hyperplasia of the parathyroid, sometimes also with secondary osteitis fibrosa. Castleman and Mallory point out that in these cases the change is a generalized hyperplasia, not adenoma formation, and that this secondary hyperplasia can be clearly differentiated histologically from primary hyperplasia. In the primary form there is a uniform differentiation of all the cells to a large water-clear type (see page 732), whereas in secondary hyperplasia the tissue is made up of normal-sized "chief cells," with a marked increase of oxyphil cells and a few small waterclear cells. It appears probable that the parathyroid hyperplasia is dependent in some way on phosphate retention by the kidneys, all the more so as a similar hyperplasia can be produced experimentally by the repeated injection of sodium phosphate.

**Hypoparathyroidism.**—The clinical manifestation of this condition is tetany. Tetany may be produced in a variety of ways, all of which are connected directly or remotely with the low calcium in the tissues. Pure parathyroid tetany is best seen when the parathyroids have been removed intentionally in animals or unintentionally in man in the course of an operation for goiter. There is a marked drop in the blood calcium and an increased excretion of

calcium in the urine. The phosphorus of the blood is normal or raised. The tissues are depleted of calcium, and tetany develops owing to the increased neuromuscular irritability. This hyperexcitability is shown by twitching of the muscles and severe clonic spasms and convulsions. When the nerves are stimulated electrically and even when pressed upon, the muscles may go into a persistent tetanic spasm.

### PARATHYROID TUMORS

These tumors have a geographical distribution which is worthy of note. Although always somewhat of a rarity, they are much commoner in the North Atlantic States, Scandinavia and England than in Italy or France. There are far more cases in the eastern United

States than in the central states. Wilder and Howell suggest that the difference is due to the absence of the ultra-violet light stimulus in gloomy and highly industrialized (smoky) countries, thus putting a strain on the parathyroids which stimulates them to tumor formation. The tumor is usually an adenoma, sometimes a carcinoma. The normal parathyroids are composed of oxyphil cells and basophil or chief cells. It is probable that the former are derived from the *latte*. The adenoma may be composed mainly of either of these types of cell. The cells are usually large and clear (water-clear or "wasserhelle" cells), presenting a vesiculated or ballooned appearance owing to their

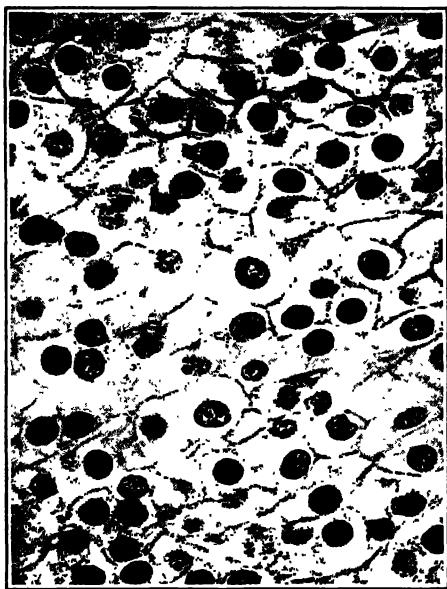


FIG. 394.—Parathyroid adenoma. The clear appearance of the cytoplasm is due to glycogen.  $\times 500$ .

rich glycogen content, and arranged in cords or columns. (Fig. 394.) The tumor may be of considerable size, in one case weighing 60 grams. Although large it may lie so deep that it cannot be palpated even though it is suspected, as in a case described by Hunter and Turnbull, where the tumor measured 7.5 cm. and yet could not be felt. Acini containing colloid may be present and the stroma may be rarefied, so that it is easy to mistake the microscopic picture for that of a degenerating thyroid adenoma, especially if the tumor is embedded in the thyroid as sometimes happens. Occasionally there are bilateral tumors. Albright, together with Castleman and Mallory, describes *hyperplasia* of the parathyroids rather than tumor in certain cases of hyperpara-

thyroidism. All the parathyroids are diffusely enlarged, in contrast to the limited and localized enlargement of adenomas. The cells, which are of the water-clear variety, are extremely uniform in type, whereas in adenoma the cytological picture is usually more varied.

**Symptoms.**—The symptoms of parathyroid tumors are those of hyperparathyroidism, and are similar to those produced by parathyroid extract. The bones are softened and rarefied, and the decalcification is readily recognized in the roentgen-ray picture. The softened bones become greatly deformed, the legs are bent, the pelvis wedge-shaped, and there is scoliosis and loss of height. Multiple tumor-like swellings of the bone are common. These show the structure of a giant-cell tumor, the giant cells probably representing a foreign-body reaction to the disintegration of bone. The bone becomes replaced by fibrous tissue, and multiple cyst formation is common. The calcium removed from the bones appears in the blood, so that the blood calcium is raised from the normal 10 mg. per 100 cc. to 15 or 18 mg. The phosphorus on the other hand is low. The plasma phosphatase, an enzyme capable of splitting certain inorganic phosphates, is considerably raised. As the tissues are rich in calcium the muscles are hypotonic, having a low electrical excitability, and there is great muscular weakness. Large quantities of calcium are excreted in the urine, so that there is a negative calcium balance which is at once rectified when the tumor is removed. The calcium is deposited in the arteries, and in the renal pelvis in the form of calcium stones. There is often a fine spotty calcification of the renal tubules.

The classical picture of osteitis fibrosa cystica is rare and easy to recognize. Other slighter and less typical manifestations of hyperparathyroidism are much more common. The condition should be suspected in every case of renal calculus. The calculus cases due to parathyroid tumor are more often not associated with bone disease than with it. The replacement of the marrow by fibrous tissue may lead to anemia and leucopenia. Bone pain and tenderness may be present for a long time before deformities appear. Multiple myeloma and metastatic carcinoma in the skeleton may give a similar picture of decalcification of bone with high blood calcium, but the blood phosphorus is also high, thus distinguishing the condition from hyperparathyroidism. In one of my cases of secondary carcinoma of bone the blood calcium was above 18 mg. per 100 cc. Senile osteoporosis is the most difficult condition to differentiate from mild hyperparathyroidism.

**Other Parathyroid Lesions.**—Many other lesions of the parathyroid glands have been reported, but none of them appears to be of any importance. Hemorrhage may occur into the parathyroids of the child during labor, but enough tissue is left to perform the normal function of the glands. Even when all four parathyroids have been destroyed by secondary carcinoma, there have been no symptoms of tetany. Fibrosis and scarring is often found in elderly persons. Cysts are not uncommon. In none of these cases is there any evidence of functional disturbance.

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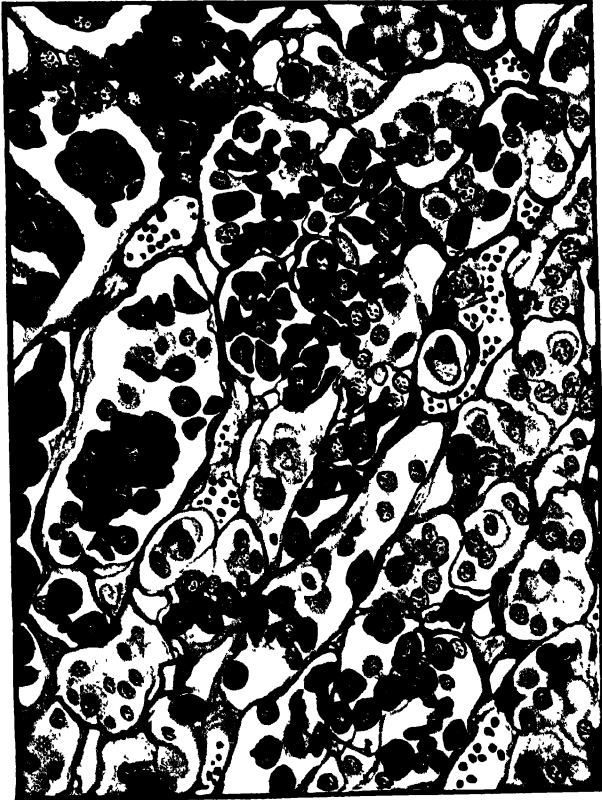
## THE PITUITARY GLAND

**Pathological Physiology.** --“Here in this well-concealed spot, almost to be covered by a thumb-nail, lies the very mainspring of primitive existence, vegetative, emotional, reproductive.” In these striking words Harvey Cushing describes the pituitary body, one of the smallest of the endocrines, but the master gland of the body. The pituitary consists of an anterior lobe and a posterior lobe. The anterior lobe is epithelial in structure, and is derived from Rathke's pouch, an up-growth from the pharynx. The stalk connecting it with the pharynx disappears, but epithelial rests may remain from which tumors may arise known as Rathke pouch tumors or craniopharyngiomas. The posterior lobe, of nervous structure, is developed from the floor of the third ventricle, and remains attached to the hypothalamic region of the brain by a stalk or infundibulum, in which a very narrow channel of communication with the ventricle remains open. The posterior lobe consists of a pars nervosa and a pars intermedia. The pars nervosa consists of non-medullated nerve fibers, which connect the pituitary with the hypothalamus, and a varying amount of nerve cells and neuroglia. The pars intermedia is an epithelial investment of the pars nervosa, derived from Rathke's pouch. It is composed of basophil cells. The active principle of the posterior lobe may be derived in part from the cells of the pars intermedia.

The *anterior lobe* contains three types of cell (Plate XXI): (1) Acidophil or eosinophil cells, with granules staining red with eosin. These cells seem to govern the growth of the body. (2) Basophil cells, with granules staining with hematoxylin. These cells are perhaps concerned with sexual development, but of this there is no definite proof. The eosinophil and basophil cells are classed together as chromophil cells. (3) Chromophobe cells with non-granular cytoplasm which stains faintly. In some pituitaries it is easy to distinguish between the three types of cells with ordinary hematoxylin and eosin staining, but in others it is extremely difficult to be certain which cells are basophil and which are chromophobe. I have found a combination of orange G, aniline blue and hematoxylin, as recommended by Rasmussen, excellent for this purpose. The proportion of the various forms is roughly as follows: chromophobe, 50 per cent; acidophil (eosinophil), 40 per cent; basophil, 10 per cent. The proportion of cells varies greatly in different sections from the same gland, so that it is difficult to speak of a normal picture; serial sections are really necessary to determine with accuracy the predominant cell. Moreover it is probable that the proportion is constantly changing. Studies on the Golgi apparatus suggest that there are only two fundamental cells, acidophil and basophil, both of which arise from chromophobes (Severinghaus). The chromophobes are of two types which can be distinguished by their Golgi apparatus; one of these develops into an acidophil, the other into a basophil. The pituitary becomes enlarged during pregnancy, and it is heavier in multiparæ than in nulliparæ and males.

The anterior lobe, being glandular in structure, is the active part of the gland, and appears to be one of the most important organs in the body. It is essential to life, as shown by extirpation experiments. It is the first of all the ductless glands to become differentiated in the course of development. It governs connective-tissue growth, in particular that of the bones, mental development, and the development of the reproductive organs. The influence of the pituitary on skeletal growth has been proved both by physiological and pathological observations. It also controls the development of the reproductive organs, both male and female. Removal causes complete atrophy of the male and female gonads. Conversely castration is followed by an increase

## PLATE XXI



Normal Pituitary Gland.

The acidophil (eosinophil), basophil and chromophobe cells are present in normal proportions. (Acid fuchsin and methylene blue.)



in the number and size of the basophils and their conversion into the so-called "castration cells" which have a signet-ring appearance owing to the presence of large colloid vacuoles in the cytoplasm.

In addition to (1) the growth-producing and (2) the gonadotropic hormones, Evans, in an excellent review describes (3) lactogenic, (4) thyrotropic, (5) diabetogenic, and (6) adrenaltropic hormones. The thyrotropic hormone can produce exophthalmos experimentally. Removal of the anterior pituitary relieves experimental diabetes, and implantation of the gland then causes hyperglycemia. Removal of the anterior pituitary reduces the adrenal cortex to a mere shell, a condition which can be cured by giving pituitary extract. From this review it is evident that the anterior pituitary is the master gland of the body. At the same time it is not a dictator insensitive to influences from those presided over, for the administration of œstrin can produce a chromophobe pituitary adenoma just as it can produce cancer of the breast.

The *posterior lobe* has never been proved to have any physiological activity, but it yields an extract of remarkable pharmacological potency. It is highly improbable that the active principles of this extract come from the inert *pars nervosa*; they appear to be produced by the *pars intermedia*, and pass *via* the pituitary stalk to the hypothalamic centers and to the cerebrospinal fluid of the third ventricle. The crude extract is known as *pituitrin*, but it contains several hormones with different actions, of which the most important are the *vasoconstrictor*, the *oxytocic* and the *antidiuretic*. The *vasoconstrictor* effect is part of a general contraction of plain muscle throughout the body; the renal vessels are somewhat relaxed in an animal under general anesthesia, so that the flow of urine may be increased, but the extract is not a diuretic, as was at one time believed. The *oxytocic* effect (*oxus*, quick; *tokos*, birth) is a contraction of the uterine muscle, which becomes very marked toward the end of pregnancy and may readily produce abortion. It would seem as if the anterior lobe of the pituitary by stimulating ovulation prepared the way for pregnancy, while the posterior lobe secretion terminated pregnancy by expelling the fetus. The *antidiuretic* effect may be very marked, particularly in diabetes insipidus. It is probably not a vasomotor action, but an effect on the epithelium of the renal tubules, as a result of which there is increased absorption of water so that the urine becomes much concentrated as well as diminished in amount.

The cells of the *pars intermedia*, which appear to provide the active principle of the posterior lobe, become basophilic when ripe, are cast off, and invade the *pars nervosa* where they are changed into hyaline bodies which pass through the loose neural spaces to the infundibulum. This "basophilic invasion of the posterior lobe" becomes more prominent with advancing years; it bears no relation to hypertension as was at one time suggested.

The intimate *relationship of the pituitary to the diencephalon* (thalamencephalon) with its hypothalamic centers and tuber cinereum in the floor of the third ventricle appears to be of the greatest importance. Non-medullated nerves pass between the hypothalamic centers and the posterior lobe, and it is probable that the secretion of the *pars intermedia* passes along the infundibulum to the hypothalamus, where it may act directly on the nerve centers or may enter the third ventricle. Removal of the superior cervical sympathetic ganglion in the dog is followed by marked movement of the pituitary colloid into the hypothalamus, the ganglion cells of which become impregnated with colloid (Popják). The hypothalamus and in particular the tuber cinereum may act as a regulator of pituitary activity. Cushing remarks that if the pituitary sex hormone is the motor that starts the reproductive cycle going, the emotional self-starter is probably in the diencephalon. The hypothalamus is the pacemaker of metabolic and emotional rhythm, governing the regularity of the rhythm of breathing, the exact maintenance of body temperature, the water balance, the cycle of sleep, and the ebb and flow of the menstrual function. A few years ago experimental work tended to direct attention away from the pituitary to the hypothalamus, and according to the "hypothalamists" many symptoms which had formerly been attributed to disease of the pituitary

were in reality caused by lesions of the diencephalon. It seems better to avoid either extreme, and to regard the posterior pituitary and the diencephalon as forming one unit with reciprocal relations. The diencephalon is the most ancient part of the cerebrum which has remained almost unchanged in the course of development, and it appears to contain the centers for the primitive elemental sensations of hunger and thirst. Experimental injury of the hypothalamus and particularly of the tuber cinereum may be followed by the development of polyuria and thirst, a condition which corresponds to the clinical state of diabetes insipidus, or by marked adiposity. Experimental lesions of this region may also be attended by pathological sleep, as if some sleep-governing center had been involved. Hypothalamic tumors, suprasellar tumors pressing on the hypothalamus, and tumors of the third ventricle may sometimes give rise to a hypothalamic syndrome characterized by one or more of the above symptoms, *i. e.*, polyuria, adiposity, and pathological somnolence. The hypothalamic centers are peculiarly liable to be attacked by the virus of epidemic encephalitis, and diabetes insipidus and other hypothalamic symptoms may develop as a result of this infection. Narcolepsy (periodic somnolence) is probably hypothalamic in origin.

Pituitary tumors may also be marked by any of these symptoms, and adiposity of a feminine type in particular is commonly regarded as a pituitary symptom. It is possible that in these cases the symptoms are really hypothalamic in origin. A pituitary tumor may burst through the membranous roof of the sella and press directly on the diencephalon. Even if this does not occur it must be remembered that the diencephalon and posterior pituitary apparently form a single functional unit, and that a lesion of the posterior lobe may well influence the hypothalamic centers through the nerve paths which connect the two elements of the unit. A clamp placed on the infundibulum which cuts off the flow of pituitary secretion to the diencephalon without interfering with the blood supply to the pituitary may cause marked adiposity. The polyuria of an experimental hypothalamic lesion or naturally occurring diabetes insipidus may be checked in a remarkable manner by the use of posterior lobe extract. In spite of these facts pointing to the functional as well as structural unity of the diencephalic-hypophyseal mechanism it seems justifiable at present to regard polyuria, adiposity, and hypersomnolence as hypothalamic symptoms, although often occurring in pituitary disease.

**Hyperpituitarism.**—With this brief review of the perplexing but all-important subject of pituitary physiology we may endeavor to outline some of the clinical features of underactivity and overactivity of the gland and to determine the lesions which may give rise to this alteration of function. In discussing these clinical features it must be borne in mind that the cause of the disturbance of function is often a tumor, an adenoma, and that this tumor in addition to elaborating an excess of the hormone normally produced by its cells of origin will usually destroy the other types of cell. Even in the purest forms of hyperpituitarism we shall not expect to find an exaggeration of all the normal functions of the gland. There will nearly always be some insufficiency to mar the perfect picture. The main effect of hyperpituitarism is excessive growth of the connective tissues and especially of the bones. If this occurs before ossification is completed the result is gigantism; if after that process is completed, the result is acromegaly.

**Gigantism** is always due to pituitary hyperplasia. A definite tumor is usually present with enlargement of the sella turcica, but in the milder forms there may merely be hyperplasia of the anterior lobe. Associated with the skeletal overgrowth there may be a later develop-



ment of symptoms of pituitary insufficiency, especially impotence in men and amenorrhea in women. The skeletal overgrowth is caused by hyperplasia of the eosinophil cells of the anterior lobe, while the subsequent sexual insufficiency is due to pressure on the cells of that lobe which are concerned with sexual stimulation (probably basophil cells). The pituitary activity may inhibit the action of insulin so that glycosuria develops, and it is common for giants to die with symptoms of diabetes. Later in the disease the tumor may be converted into a cyst so that the pituitary is greatly shrunk, but the skeletal changes are permanent, and the expanded sella bears witness to the former size of the gland.

*Acromegaly* is the result of hyperpituitarism after ossification is completed. The chief changes are enlargement of the bones, hypertrophy of the connective tissue, and changes in the skin and hair, to which may be added later in the disease symptoms suggestive of hypopituitarism such as depression of the sexual function. The tumor found at operation or autopsy is more often a chromophobe than an acidophil adenoma, but it is probable that the cells were acidophil in the early phase of the disease. It was Pierre Marie who, in 1886, recognized the pituitary origin of the disease and named it from the great enlargement of the hands and feet (*akros*, extremity; *megale*, large). The face is large, the frontal sinuses prominent, the eyes deeply set, the lower jaw is heavily undershot and prognathous so that the lower teeth project beyond the upper ones, the teeth themselves are widely separated, the hands and feet are huge and clumsy with exostoses on the phalanges and a characteristic tufting of the terminal phalanx seen in the roentgen-ray picture. Kyphosis may be marked, and the patient with his bent back, huge hands reaching to the knees and protruding lower jaw presents a gorilla-like picture. In addition to the osseous changes there is marked connective-tissue hyperplasia which produces enlargement of the lips, tongue, nose, hands, and feet. Owing to this fibrosis the skin becomes thick, coarse, and furrowed, a change that is most strikingly evident in the scalp which is deeply corrugated like that of a bulldog. There is marked increase in the hair, which is thick and coarse, and profuse sweating is common. In the active stage of the disease there may be increased sexual excitement. Lactation after pregnancy may continue for a number of years. Changes in the basal metabolic rate are not constant, but during the active stage it may be increased and the appetite is sometimes voracious. Glycosuria occurs in about 20 per cent of the cases, but it is curiously inconstant in the same patient. The disease is self-limited, and the signs of overactivity become replaced by those of hypopituitarism, *i. e.*, adiposity, somnolence, and sexual impotence. The structural changes (bone and connective tissue) are of course permanent.

**Hypopituitarism.**—This is a much commoner condition than hyperpituitarism, but the clinical manifestations are more varied and confusing, and the lesions to which the deficiency of pituitary secretion may be due are correspondingly varied. Three fairly well-defined

types may be recognized, named respectively the *Fröhlich type*, the *Simmonds type*, and the *Lorain type*.

1. The *Fröhlich syndrome*, which is the common form, is a dystrophia adiposo-genitalis that commonly develops about the time of puberty, but may appear later in life. Depression of the sexual function is the earliest and most constant symptom. There is amenorrhea in the female, due to absence of the hormone which stimulates ovarian function, and loss of libido in the male. The sexual organs remain undeveloped or atrophy. Of equal importance is atrophy of the skin and hair, in striking contrast to what is found in acromegaly. The skin is thin, delicate, smooth like a child's and dry. This is due to atrophy of the dermal connective tissue. The hair of the head is normal in amount but soft and fine; the facia, axillary and pubic hair is scanty; the skin of the trunk and legs is hairless. After the age of thirty-five years the soft skin becomes finely wrinkled owing to the lack of fibrous tissue in the dermis. Adiposity may be very marked or may be absent. When the condition develops in an adult male, deposits of fat in the breasts, hip, buttocks, and lower abdomen give the figure a distinctly feminine cast. Sudden fluctuations of weight are characteristic. The basal metabolic rate is usually low. Mental dulness of varying degree is common. Sugar tolerance is not really high as is commonly supposed, for after the administration of glucose the blood-sugar curve takes an unusually long time to return to normal owing to the general slowing up of metabolic processes, but glycosuria never occurs, so that in that sense the patient has a good sugar tolerance. A variation of this syndrome is the adipose type, illustrated to perfection by the Fat Boy in *Pickwick*. His face is round and chubby, his mind is slow, and he is ready to drop asleep at a moment's notice.

Another rare and remarkable variation of the *Fröhlich type* is known as the *Lawrence-Biedl syndrome*. This is characterized by a strong familial tendency, adiposity, genital dystrophy, mental deficiency, retinitis pigmentosa, and polydactylism. A patient with adiposity, partial blindness, and six fingers or six toes is easily recognized as belonging to this group, especially when it is found that other members of the family present the same condition.

2. The *Simmonds syndrome* may develop in adult life or in childhood. Both are examples of premature senility or *progeria*. When the disease appears in childhood the patient remains a dwarf. A person suffering from pituitary old age presents a remarkable clinical picture, for a child of ten may have the aspect of a decrepit old man. There is a general microsplanchnia, all the organs being small and under weight in contrast to the large heavy organs of acromegaly. The atrophy may affect the thyroid causing thyroid insufficiency (myxedema), or the adrenals causing adrenal insufficiency. Extensive ischemic necrosis of the anterior pituitary is not uncommon in women during delivery due to thrombosis of the pituitary vessels caused by collapse after severe hemorrhage (Sheehan). It is probable that such necrosis is the usual cause of Simmonds' disease in adults. The clinical picture described above is an extreme one, and in cases with slighter degrees of pituitary necrosis there may be neither emaciation nor premature senility, but such features as amenorrhœa, breast atrophy, easy fatigability, and symptoms of mild myxedema.

3. In the *Lorain type* the patient is bright mentally, but remains small and undeveloped sexually. When he grows up he remains like a graceful and

attractive child. Peter Pan might be placed in this group. This type may be called pituitary dwarfism, just as the Simmonds type may be called pituitary senility.

The *lesions in hypopituitarism* are varied. The usual organic cause is craniopharyngioma. Such tumors press upon the hypothalamus as well as upon the pituitary, and as they are congenital in origin and usually develop early in life, they cause some of the most extreme forms of adiposogenital dystrophy in children. Chromophobe-adenoma of the pituitary may sometimes be responsible. This seldom develops before the age of twenty years, and therefore fails to explain the cases occurring in childhood. As the adenoma is often confined to the sella and therefore may not press on the hypothalamus, adiposity may be slight or absent. Another not infrequent lesion is a suprasellar tumor, either a glioma of the chiasma or the much commoner cranio-pharyngioma. Such tumors press upon the hypothalamus as well as upon the pituitary, and as they are congenital in origin and usually develop early in life, they cause some of the most extreme forms of adiposogenital dystrophy in children. A much rarer group is that of pituitary infarction or ischemic necrosis (Simmonds), where the primary lesion is a vascular occlusion. Many of these cases of pituitary old age have been attributed to puerperal sepsis. In other cases nothing is found beyond a hypoplasia of the pituitary, which is indicated clinically by the very small size of the sella turcica. In addition to these gross organic causes there can be little doubt that in many, indeed the majority of cases, there is no tumor nor necrosis, but merely a hypofunction of the gland, often temporary in character, as a result of which there may be some retardation of growth, lack of sexual development, or undue adiposity, all of which may be remedied in the course of a few years.

**Dyspituitarism.**—This name is given to those cases which present a mixed picture, in part suggesting hyperfunction and in part hypofunction. The patient may be fat and hairless, and yet may have large accessory nasal sinuses, prominent supra-orbital ridges, and other stigmata of acromegaly. In some of these cases a mixed type of tumor (chromophil chromophobe) is found; others are examples of overactivity followed later by underactivity.

## TUMORS OF THE PITUITARY GLAND

A tumor of the pituitary is an adenoma, usually innocent, rarely a malignant adenoma. It may be debated whether the common adenoma is a true tumor or merely a glandular hyperplasia, but from the practical standpoint it must be regarded as a tumor, the most serious effect of which is often the pressure which it produces. Pituitary adenomas may be divided into three types: (1) chromophobe, (2) acidophil, and (3) basophil.

**Chromophobe Adenoma.**—This is much the commonest form of pituitary tumor. The chromophobe cells are non-granular, so that the

cells of the tumor appear clear. Most of these tumors show a very characteristic alveolar grouping, with fibrous septa between the groups (Plate XXII), but in some the cells are arranged diffusely. The type of tumor can usually be recognized by this alveolar arrangement without having recourse to a special study of the granules. The tumors about to be described are those which produce symptoms either local or general. Much more common are collections of cells which have been called subclinical adenomas (Costello), usually miliary or microscopic in size and producing no symptoms. The cell pattern differs from the normal and may be that of a convoluted papilloma or a compound tubular gland. These cell collections are not encapsulated. When symptoms are present they are those of pituitary insufficiency, similar to the changes produced in an animal when the anterior lobe is removed. Chromophobe cells are parent cells of eosinophils and basophils, and their overgrowth apparently gives rise to no positive symptoms. The negative symptoms of insufficiency are the result of compression of the more actively functioning eosinophil and basophil cells. The adenoma often remains confined to the sella, causing interference with skeletal and sexual development. If it breaks through the membranous roof and presses on the tuber cinereum, hypothalamic adiposity will be superadded.

**Acidophil Adenoma.**—The eosinophil adenoma is a good deal less common. It is composed of cells filled with red-staining granules (Plate XXIII), the cells are large and often multinucleated, and they are arranged diffusely, with complete absence of the alveolar grouping so characteristic of the chromophobe adenoma. The eosinophil cells are concerned with skeletal growth, so that the tumor is associated with the syndrome of overgrowth, *i. e.*, gigantism or acromegaly. The acidophil adenoma may give rise to the nearest approach to pure hyperpituitarism (skeletal overgrowth, connective-tissue hyperplasia, hypertrichosis, glycosuria, increased metabolic rate), but later in the disease insufficiency symptoms become apparent. It has already been remarked that the tumor found at autopsy is often a chromophobe adenoma, but it is probable that it was acidophilic in type in the earlier phase of the disease.

**Basophil Adenoma.**—This is by far the rarest form of pituitary adenoma. It is small in size, and consists mainly or wholly of basophil cells. In 1932 Cushing described a highly characteristic clinical picture, since known as *Cushing's syndrome*, marked by the following features: (1) painful adiposity which is confined to the face, neck and trunk, but spares the limbs (buffalo type of obesity); (2) hirsutism of the face, neck and trunk in females, preadolescence in males; (3) dusky plethoric appearance; (4) peculiar striations of the skin which give the abdominal wall, both male and female, an appearance of pregnancy; (5) sexual dystrophy (amenorrhœa in females, impotence in males); (6) kyphosis of the upper thoracic spine; (7) vascular hypertension; (8) a tendency to diabetes, as well as other features which will be found in Cushing's original paper.

PLATE XXII

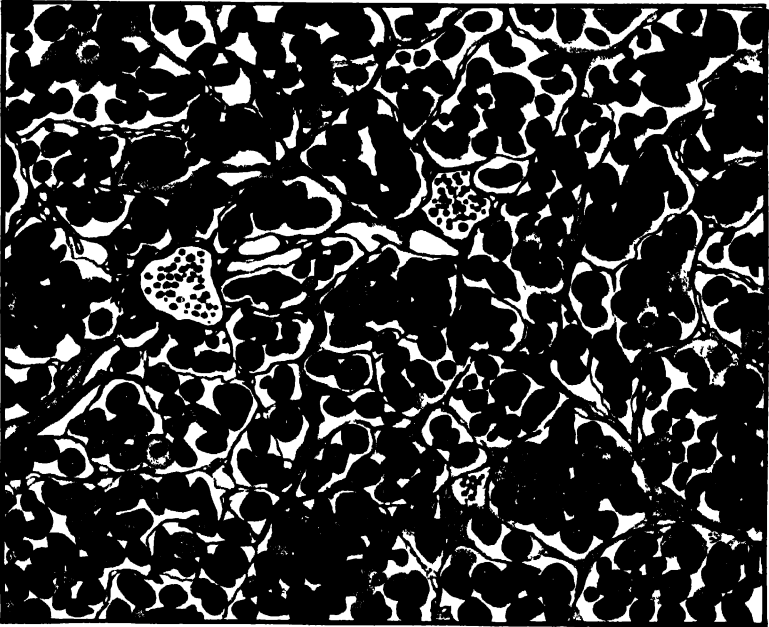


**Chromophobe Adenoma of Pituitary.**

The pale cells show a definite alveolar grouping. Four acidophil cells are present.



PLATE XXIII



Eosinophil (Acidophil) Adenoma Pituitary.

The cytoplasm of the cells is intensely red compared with that of the red blood cells in the capillaries. The arrangement is much more diffuse than in the chromophobe adenoma.





Cushing attributed this remarkable clinical picture to a basophil adenoma of the pituitary which was present in a number of his cases. It is now known that this idea is erroneous. Basophil adenomas are often found unassociated with the syndrome, and the syndrome occurs apart from basophil adenoma. There is, however, one constant finding in the pituitary, namely a hyalinization of the basophil cells with disappearance of their granules, first described by Crooke in 1935. Instead of the condition being a manifestation of overactivity of the basophil cells (basophilism), it appears rather to be the result of inactivity of these cells (Heinbecker). The hyalinization is an indication of such hypofunction. Loss of the basophil cells leads to regressive changes in the thyroid, gonads and islets of Langerhans, which are probably responsible for some of the protean manifestations. The occurrence of small basophil adenomas may indicate merely an attempt to compensate for the depressed basophil function. Heinbecker, in an excellent review of the subject, points out that at least three primary lesions may be precursors of the all-important hyalinization of the basophil cells; these are (1) a tumor of the adrenal cortex, (2) a tumor of the thymus, and (3) atrophy of the nuclei of the hypothalamus. Experimental lesions of the hypothalamus in the dog are followed by marked loss of basophil cells with degenerative changes in the remaining basophils. The most frequent primary lesion is a tumor (usually a benign adenoma) or hyperplasia of the adrenal cortex. Every case of Cushing's syndrome should therefore be explored for adrenal tumor.

**Malignant Adenoma.**—This is a rare condition. In Cushing's series there were only 3 malignant tumors compared with 159 innocent ones. The tumor destroys the base of the skull, bursts through the roof of the sella, and invades the floor of the third ventricle. The cells, which are of the chromophobe type, are grouped in irregular masses.

**Neighborhood Symptoms.**—The effects of a pituitary tumor may be divided into general tumor symptoms, endocrine symptoms, and neighborhood symptoms. The first group comprises the symptoms of cerebral tumor in general, particularly increased intracranial pressure. If the tumor is small and confined to the sella these symptoms will be absent. The endocrine symptoms have already been discussed. The neighborhood symptoms are caused by pressure on neighboring structures. Pressure on the optic nerve causes optic atrophy of the primary type. The most characteristic pressure symptom is bitemporal hemianopsia due to compression of the inner fibers of the optic chiasma. There may be pressure on the hypothalamus with production of the hypothalamic syndrome (adiposity, polyuria). This is more likely to be caused by a chromophobe than a chromophil adenoma, as the latter remains confined to the sella long after the development of symptoms of hyperpituitarism. The sella is always expanded by the tumor, and may be markedly ballooned, with absorption of the clinoid processes.

**Craniopharyngiomas.**—Tumors of Rathke's pharyngeal pouch or the hypophyseal duct, conveniently called craniopharyngeal tumors, arise from vestigial remnants of the epithelial tract from which the anterior lobe of the pituitary is originally formed. They are usually suprasellar tumors, but may originate and be confined within the sella. They may be quite minute, about the size of a pea, or may form huge

calcareous masses as large as a tennis ball. The tumor usually appears under the age of fifteen years, and attains a much larger size than the average pituitary adenoma. Cystic degeneration and calcification of the wall of the cyst are common, and suprasellar calcification (*x-ray*) is a clinical sign of great value. The tumor may compress the pituitary, causing retardation of growth, but the most marked symptom may be adiposity due to pressure on the hypothalamus. The most typical form of Fröhlich's syndrome in tumors is produced by Rathke pouch tumors. Microscopically the tumor is usually an epidermoid carcinoma, but it may be a basal-cell cancer of the adamantinoma type. Cystic degeneration is common, and the entire tumor may be converted into a cyst.

**Dermoid Tumors.**—Dermoid tumors are of rare occurrence in this region. They are due to invagination of the cranial epidermis during closure of the neural canal.

**Congenital Anomalies.**—The anterior lobe of the pituitary is formed from a diverticulum from the roof of the buccopharyngeal junction. A remnant of this process is practically constant under the pharyngeal mucosa, where it is known as the pharyngeal hypophysis. Other remnants may be left along the course of the craniopharyngeal canal where they may give rise to the craniopharyngiomas. Congenital hypoplasia of the gland is found in various types of dwarf.

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## CHAPTER XXIX

### THE LYMPHOID STRUCTURES

#### THE SPLEEN

**Descriptive Outline.**—In describing the spleen consider the size, weight, color, consistence, and cut surface. The *size* varies much within normal limits, depending on age, physiological state, etc. The average length is about 12 cm., the breadth 7 cm., and the thickness 3 cm. In old age the spleen becomes atrophic, and the shrinking of the organ leads to wrinkling of the capsule which is also thickened. The *weight* is 150 to 200 grams. The *color* is a reddish-purple. The *consistence* is pliable (not really soft) and somewhat friable. On the *cut surface* the fibrous trabeculæ are seen as thin white lines, and the Malpighian bodies as pale gray spots about 1 mm. in diameter. In the senile spleen the fibrous framework is greatly increased. The microscopic study of the spleen is difficult for the student and also for the expert. The picture is confused and nothing appears to be clean cut. It will help if attention is paid to the following: (1) lymph follicles (Malpighian bodies) together with the arterioles which they surround, (2) pulp, (3) sinusoids, and (4) trabeculæ. The arterioles frequently show a hyaline thickening, especially with advancing years; this is of less pathological significance in the spleen than in any other organ. The sinusoids can hardly be seen in health; in disease they may be dilated and the lining cells become prominent. The normal trabeculæ are often mistaken by the student for pathological fibrosis.

**Physiology.**—It is usual to regard the spleen as a great reticulo-endothelial sponge with a supporting framework of trabeculæ and reticulum and a certain amount of lymphoid tissue superadded. Such a structure is designed to detain and alter the blood which slowly percolates through it. When the blood has traversed the arterioles it flows out into the wide mesh of the splenic pulp, from which it is collected into venous sinusoids. The walls of these sinusoids are fenestrated in a remarkable manner so that the cells wandering through the pulp may enter these venous channels in the freest manner. The effect of the whole arrangement is to bring the cells of the blood into the most intimate contact with the elements of the reticulo-endothelial sponge.

A rather different conception of splenic physiology is afforded by Knisely's direct microscopic observations of living transilluminated mammalian spleen. By this technique the sinusoids appear to be separated by partitions of pulp and lined by walls which are readily permeable to fluid and colloids but not to red blood cells. There seems to be a phase of storage of blood and a phase of flow, the flow being regulated by sphincters situated on the arterial and venous sides of the sinusoids. The cycle begins with closure of the sphincter on the venous side, as a result of which the sinus becomes distended with blood and fluid passes through the wall into the pulp. When the sinus

is completely distended with red cells the sphincter on the arterial side shuts, and the corpuscles lie free from plasma for a varying period, sometimes up to ten hours. The sphincter on the venous side then opens, and a soft mass of red cells passes into the vein. During the phase of storage or separation the erythrocyte-plasma interface is profoundly changed, as a result of which the cells become spherical instead of biconcave and are therefore more readily hemolyzed. The importance of these observations becomes evident when hemolytic anemia is considered. Knisely claims that many of the appearances seen in microscopic sections, such as infiltration of the pulp with red cells and slits in the sinus wall through which cells can pass, are due to rapid agonal changes.

The suggested *functions* of the spleen are varied. These are: (1) a filter for bacteria and the iron of worn-out erythrocytes; (2) a former of antibodies; (3) a manufacturer of blood in conditions such as pernicious anemia and osteosclerotic anemia; (4) a reservoir or bank for red cells, undoubtedly true for certain animals, but doubtful in the case of man.

### INFECTIONS OF THE SPLEEN

**Acute Splenitis.**—There is no organ which can so rapidly change its size as the spleen. The normal spleen weighs about 150 grams, but in acute infections it soon becomes two or three times that size. It is not likely to be palpable until it is about three times the normal size, especially if it is soft. This acute enlargement is often called acute splenic swelling or acute splenic tumor. The most striking examples are shown by what may be termed the *septic spleen*, which is seen in pneumonia, septicemia, acute endocarditis, and other acute infections. It is enlarged, often very soft, and of a grayish-pink color. The pulp swells up in a pouting fashion on the cut surface, and is so soft that it can be wiped away with the knife. The softest spleens are seen in septicemia and pyemia. The swelling is due partly to enormous numbers of cells trapped in the pathless forest of the pulp, partly to local proliferation. Rich and his associates have shown by motion picture studies of tissue cultures that the large, basophilic, mononuclear cells which predominate have the same method of locomotion as lymphocytes, and are therefore probably lymphoid in character. In *typhoid fever* the spleen is enlarged so as usually to be palpable, soft, and deep red in color. The cut surface may resemble red jelly. The splenic pulp and sinuses are crowded with red blood corpuscles, together with large numbers of the macrophages characteristic of typhoid infection. Many of the macrophages contain erythrocytes which have been phagocytosed. In diphtheria and other acute infections of childhood there may be marked swelling of the lymph follicles so that they become visible to the naked eye.

**Tuberculosis.**—Tuberculosis of the spleen is of little importance. In general miliary tuberculosis the spleen is enlarged and may be studded with tubercles, which are easily mistaken for enlarged lymph follicles. Occasionally

large caseous masses are scattered throughout the spleen causing marked enlargement of the organ. The primary lesion in the lung or lymph nodes may be so small and quiescent that it is readily overlooked, and the condition is described as primary tuberculosis of the spleen. A large solitary tubercle (tuberculoma) is of very rare occurrence.

**Syphilis.**—In congenital syphilis the spleen is frequently enlarged and contains large numbers of spirochetes. The condition is often associated with marked anemia. Syphilitic enlargement of the spleen is rare in adults and difficult to diagnose. It may be due to the formation of gummata, but more often the only change found is a diffuse fibrosis.

**Malaria.**—Enlargement of the spleen is one of the commonest lesions in malaria. In an acute attack the spleen is moderately enlarged and soft, but as a result of long-continued infection it becomes greatly enlarged and very hard (*ague-cake spleen*). In malarial districts the greater part of the population may have enlarged spleens, giving the children in particular a pot-bellied appearance.

**Kala-azar.**—Kala-azar is a common cause of splenomegaly in the tropics. The spleen is very greatly enlarged, fibrosis is marked, and the pulp is filled with macrophages containing the Leishman-Donovan parasites which have already been described in Chapter VIII. The parasites are readily demonstrated by means of splenic puncture.

**Amyloid.**—The splenic lesions have already been described in connection with amyloid disease (Chapter II). The spleen is much enlarged, elastic, and very firm. The common lesions affect the arterioles of the lymph follicles, but the fibrous reticulum is sometimes involved. The disease is almost never confined to one organ.

## CHRONIC SPLENOMEGALY

It is impossible to make any satisfactory classification of the chronic enlargements of the spleen, as so little is known regarding their real nature, but we may recognize disease conditions affecting the principal elements of which the organ is composed, *i. e.*, lesions of the vascular structures, the reticulo-endothelial structures, and the lymphoid structures. In the first group we have splenic anemia and infarction, the second group includes Gaucher's disease, Niemann-Pick's disease, hypercholesterolemic splenomegaly, and hemolytic jaundice, while in the third group there are the leukemias.

**Splenic Anemia.**—This is an example of what Eppinger calls hepatosplenic (hepato-lienal) fibrosis, an excellent term indicating that the liver and spleen form a unitary system either or both members of which may be the seat of unexplained fibrotic lesions. When the liver is principally affected the condition is called cirrhosis. When the main lesions are in the spleen the condition is called splenic anemia. *Banti's disease* is a name which has long been applied to those cases in which there is first enlargement of the spleen with anemia and leucopenia, followed later by cirrhosis of the liver with ascites and a tendency to gastric hemorrhage. This association is so variable and the clinical picture is so indefinite that little is to be gained by preserving the name. One may speak of the Banti syndrome, but it is certainly not a separate disease entity. The development of clinically evident cirrhosis of the liver in splenic anemia is an uncommon occurrence. The ordinary case displays a characteristic triad of symptoms,

i. e., splenomegaly, secondary anemia and leucopenia, and gastric hemorrhage.

The *nature of the condition* has long been a matter for discussion. Banti's view that the splenic condition was primary has become untenable, in spite of the fact that removal of the spleen may sometimes cure the condition. This is true of other diseases where the changes in the spleen cannot be regarded as fundamental (hemolytic jaundice, thrombocytopenic purpura). Evidence is accumulating that splenic anemia is a vascular disturbance of the spleen due to high portal blood-pressure. There is a valvular mechanism in the splenic arterioles at the point where they end in the ellipsoids, so that the back-pressure is not transmitted to the splenic artery, but makes its effects felt on the splenic pulp. The question of how much the spleen will enlarge depends a good deal on the age of the patient, marked enlargement occurring more readily in young persons. The cause of the heightened portal pressure is a matter of uncertainty; indeed it must be understood that the idea itself is still hypothetical. Cirrhosis of the liver is a sufficient cause, but splenomegaly usually develops long before there is any indication of cirrhosis. Measurements of the diameter of the branches of the portal vein in the liver show that there may be considerable narrowing with little or no cirrhosis in the ordinary sense of the word. Other causes of portal back-pressure are thrombosis of the portal or splenic veins, and vasodilatation of the hepatic artery. It is possible that in some cases the primary lesion may be in the spleen, a fibrosis of the Malpighian arterioles which are known to regulate the blood flow through the spleen. This would allow too much blood to enter the spleen, with resulting congestion and fibrosis.

**Lesions.**—The spleen is much enlarged and very firm. The average weight is 800 to 900 grams. The capsule is thickened, and the cut surface, from which no blood escapes, has a fibrosed or beefy appearance. The *microscopic lesions* are similar to the changes found in portal cirrhosis. The chief features are dilatation of the sinuses and thickening of the fibrous framework of the organ. (Fig. 395.) The fibrosis is periarterial in origin, extending throughout the reticulum, and finally involving the main trabeculæ. The arteries usually show hyaline degeneration, but this change is of such common occurrence beyond the first decade that it has no special significance. Periarterial hemorrhages are frequent. A common finding is the presence of yellowish-brown flecks like flakes of tobacco leaf on the cut surface. Microscopically these may present a peculiar filamentous appearance, so that the lesions have been mistaken by some observers for the mycelia of fungi. The filaments are merely elastic fibers on which iron has been deposited, and the so-called fructification organs of the supposed fungi are pale green crystals jointed together like a bamboo cane. In addition to the filaments and crystals there are masses of hemosiderin, some of which is intracellular and some extracellular, together with giant cells and deposits of calcium. The whole mass gives an intense reaction for iron, and may be called a *siderotic nodule*.

(Fig. 396.) These nodules are probably caused by hemorrhage at the point of termination of the arteriole in the ellipsoid where there is a valvular arrangement, so that raised portal blood-pressure may cause

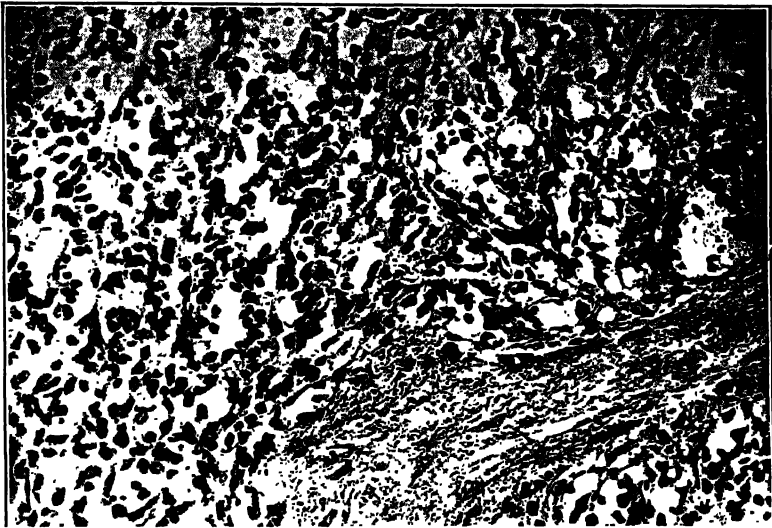


FIG. 395.—Banti's disease. General fibrous thickening of splenic reticulum and dilatation of the sinuses.  $\times 250$ .

rupture of the vessel at this point (McNee). The hemorrhage is followed by organization and fibrosis. Much of the iron-containing blood pigment is carried away by phagocytes, but some may be taken up by fibroblasts. These cells proliferate and lay down collagen fibers,



FIG. 396.—Siderotic nodule in spleen. The bamboo-shaped crystals are very characteristic.  $\times 1000$ .

and in this way the splenic reticulum becomes more and more fibrosed. All cases of splenic anemia do not show siderotic nodules, nor are the nodules confined to this disease. Their great importance lies in the

fact that they indicate an increase in the portal blood-pressure, which is the chief cause of the hemorrhages. The nodules are also found in the intensely congested spleen of hemolytic jaundice, in which hemorrhage may readily occur.

Degenerative changes in the splenic vein and portal vein are of common occurrence, and there may be thrombosis. These lesions are probably secondary to heightened portal blood-pressure. If they are sufficiently great they may produce some of the splenic changes. Thickening of the wall (phlebosclerosis), endophlebitis, atheromatous change, and calcification are the chief lesions. The vein may be greatly distended, and huge collateral channels may connect the spleen with the stomach and diaphragm. The liver may or may not show cirrhosis of the portal type, but even when there is no cirrhosis it is probable that there is narrowing of the terminal branches of the portal vein.

**The Relation of Symptoms to Lesions.** - The enlargement of the spleen is probably the result of the increased portal pressure, which causes the dilatation of the sinuses, the hemorrhages, and indirectly the fibrosis. The gastric hemorrhage, one of the most constant and often one of the earliest of the symptoms, can best be explained by the same mechanism. These hemorrhages are analogous to the siderotic nodules in the spleen. In the former the blood escapes on a free surface, while in the latter it is imprisoned within a solid organ. The cause of the anemia is unknown. The anemia, usually associated with leucopenia, is not of the hemolytic type, for there is no evidence of undue hemolysis, and the fragility of the red cells is not increased. It may not develop until long after the splenomegaly has been detected, but it appears to be related to the lesions in the spleen, for splenectomy may cure the disease if it is not too far advanced. The gastric hemorrhages may contribute to the condition, but cannot account for all the cases. Possibly there is a condition of hypersplenism, as a result of which the erythrocytes are injured, but this is a pure guess. Indeed we cannot say for certain if there is such a thing as hypersplenism, though it appears probable. It must be remembered that in portal cirrhosis of the liver a progressive anemia is the rule. The three conditions which are most benefited by splenectomy are hemolytic jaundice, thrombocytopenic purpura, and splenic anemia.

**Infarction.** - An infarct of the spleen may be caused in the usual way by embolic occlusion of the artery. If the embolus is infected an abscess will be formed in the spleen. Or it may develop as the result of vascular disturbances in the spleen (thrombosis of the splenic vein) in such conditions as splenic anemia and leukemia, and injury to the organ, especially rupture. It presents the usual characters of an ischemic infarct, but in addition siderotic nodules may be present. The infarct reaches the surface and involves the surface, in contrast to infarct of the kidney where a thin rim of uninvolved tissue separates the infarct from the capsule. This explains why pain is a symptom more characteristic of splenic infarct than of renal infarct.

**Chronic Congestion.** - The spleen may become congested and enlarged either as the result of mitral valvular disease or of portal obstruction from cirrhosis of the liver. The enlargement in mitral disease is much less than in cirrhosis, because the liver serves to take up the back-pressure, only a small proportion of which reaches the spleen, so that the enlargement can seldom be detected clinically.



The *cardiac spleen* is about double the normal size (normal weight, 150 grams), dark, and very firm owing to a gradually increasing fibrosis. The sinuses are distended, the pulp infiltrated with red blood cells, and the fibrous reticulum much increased. The lymphoid tissue tends to disappear. No siderotic nodules are found in this condition.

**Gaucher's Disease.**—This rare condition is a disorder of the reticulo-endothelial system. It commences in early life, usually in Hebrews, and is sometimes familial. There is an extreme degree of splenomegaly, moderate enlargement of the liver, some secondary anemia and rather pronounced leucopenia, a brownish-yellow coloration of the skin, and yellow wedge-shaped patches in the conjunctiva on each side of the cornea. Splenic puncture shows the very characteristic large, pale Gaucher cells. Roentgen-ray examination shows rarefaction of the bones, flattening of the head of the femur, and a fusiform expansion of the lower end of that bone. As the vertebræ are involved in the rarefaction, the stature may be stunted.

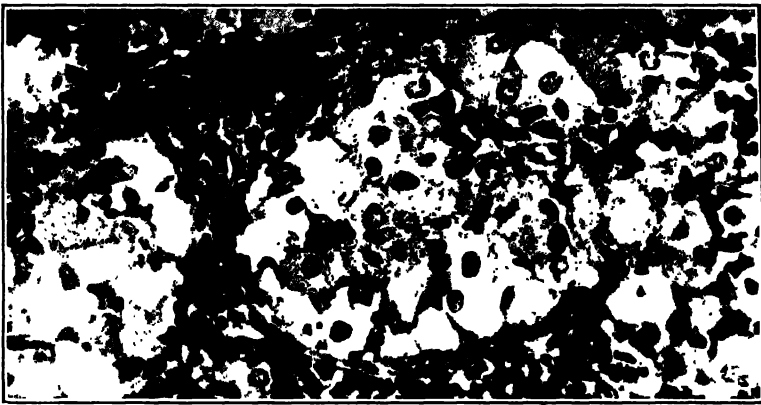


FIG. 397.—Gaucher's disease.  $\times 315$ .

The spleen may be enormous, filling the greater part of the abdomen. White spots are scattered over the surface, and these consist of very large, peculiarly pale cells filled with lipid. (Fig. 397.) These are the Gaucher cells, and represent the reticulo-endothelial cells of the organ filled with the cerebroside, kersasin. It stains feebly with the ordinary fat stains (Sudan, Scharlach), but intensely with Weigert's method designed for the more complex lipoids. It is the swelling of these cells which causes the great enlargement of the spleen. The lesions are not confined to the spleen, but are found also in the liver, lymph nodes, bone-marrow, and other parts of the reticulo-endothelial system. The anemia and leucopenia are caused by the bone-marrow lesions. In one form of Gaucher's disease the lesions are mainly osseous. All the affected members of a family may suffer from this form. Pick mentions a family in which five brothers developed skeletal lesions.

Scarcely a bone in the body may be spared. The disease is an example of lipid storage by the cells of the reticulo-endothelial system. The basis of the condition is a disturbance of lipid metabolism, the nature of which is at present unknown. Other examples of abnormal lipid storage are Niemann-Pick's disease, Schüller-Christian's disease, and hypercholesterolemic splenomegaly.

**Niemann-Pick's Disease.**—This is an even rarer condition than Gaucher's disease, of which it may be regarded as a variation. It is a familial condition, occurring nearly always in Jewish infants, and the child does not live beyond the second year. In addition to involvement of the spleen, liver, lymph nodes and bone-marrow as in Gaucher's disease, the characteristic lipid-filled cells are found in the adrenal, pancreas, thymus, intestinal mucosa, lung, brain, and renal glomeruli. The histiocytes as well as the endothelial and reticular cells are involved, so that it is a true lipid histiocytosis. Many epithelial cells may contain the lipid, *e. g.*, thyroid and kidney, and the monocytes of the blood may also be filled with this material. Widespread involvement of the ganglion cells of the brain and retina is the basis of amaurotic family idiocy. The lipid differs from that of Gaucher's disease in being a phospholipid, namely sphingomyelin.

**Schüller-Christian's Disease.**—This very rare condition is characterized by defects in the membranous bones, especially the skull, exophthalmos, and diabetes insipidus—at first sight a curious mixture. It is a disturbance of lipid metabolism in young people, with nodular yellowish-brown deposits of cholesterol and its esters in the white fibrous tissues and especially in the periosteum and dura mater. These deposits take the form of xanthoma or xanthomatosis with giant-cell formation. The bone defects are due to erosion caused by the periosteal deposits, the exophthalmos to deposits in the orbit, and the diabetes insipidus to deposits around the pituitary. The pituitary lesion may also cause dwarfism.

Gaucher's disease, Niemann-Pick's disease, and Schüller-Christian's disease are all examples of lipid storage, but the lipid is different in each case. In Gaucher's disease it is a cerebroside (kerasin), in Niemann-Pick's disease it is a phospholipid (sphingomyelin), and in Schüller-Christian's disease it is cholesterol and cholesterol ester. It has been suggested (Thannhauser) that Gaucher's disease and Niemann-Pick's disease are true examples of lipid storage due to hyperlipemia, whereas Schüller-Christian's disease is a primary essential xanthomatosis not dependent on and unconnected with hyperlipemia.

**Hemolytic Jaundice.**—This condition is considered in connection with diseases of the blood, but brief reference may be made to the condition of the spleen. The spleen is moderately enlarged, deep red in color, and the pulp is filled with red blood cells to an incredible degree, so that all traces of splenic structure disappear unless the spleen is drained of blood before being fixed. When this is done it is seen that the sinuses are relatively empty. If the spleen is removed in the active stage of the disease it is found to contain a great amount of hemosiderin, for the most part within the reticulo-endothelial cells. During the inactive stage there is little or no pigment. In this disease there is evidently a great increase in the phagocytic activity of the reticulo-endothelial cells, although the essence of the condition is an increased fragility of the erythrocytes, and the splenic enlargement is due to hypertrophy of these phagocytic cells as well as to accumulation of blood in the splenic pulp.

**Hodgkin's Disease.**—The spleen is constantly enlarged in Hodgkin's disease, but as it is a disease of the entire reticulo-endothelial system, involving liver, lymph nodes, bone-marrow, etc., it is more conveniently considered in connection with disorders of that system.

**Leukemia.**—The spleen is involved in both forms of leukemia, but the lesions will be considered in connection with diseases of the blood. Infarcts are not uncommon.

**General Review of Splenic Enlargements.**—Enlargement of the spleen may be due to very different causes. The spleen is a contractile sponge, which may rapidly undergo marked variation in size. (1) In acute splenic swellings there is a great accumulation of inflammatory cells in the pulp, to which is probably added proliferation of the local endothelium. (2) The splenomegaly of hemolytic jaundice is characterized by an enormous accumulation of red blood cells in the splenic pulp, but the condition must be regarded as a reticulo-endothelial rather than a vascular disorder. (3) In polycythemia vera the spleen is moderately enlarged and firm owing to an accumulation of the excess red cells in the splenic reservoir. There may be cystic spaces filled with blood. (4) Splenic anemia appears to be due to vascular disturbances in the spleen caused by back-pressure in the portal and splenic veins. (5) The splenic enlargement of portal cirrhosis and the much lesser enlargement in chronic valvular disease of the heart is due to a similar cause. The increase in the fibrous reticulum which occurs in these conditions may be responsible for some of the enlargement. (6) The enlargement of amyloid disease is due to the great swelling of the individual connective-tissue fibers. (7) In the lymphoblastoma group (Hodgkin's disease, lymphosarcoma and leukemia), there may be hyperplasia both of the lymphoid and the reticulo-endothelial structures in the spleen. (8) The lipoid storage diseases (Gaucher's disease, Niemann-Pick's disease, and hypercholesterolemic splenomegaly) form a group in which distention of the reticulo-endothelial cells with lipoid is attended by great enlargement of the spleen. (9) The splenomegaly of kala-azar and possibly of malaria is due to a reticulo-endothelial proliferation. (10) The moderate enlargement in pernicious anemia may be due to myeloid transformation of the pulp.

## OTHER LESIONS OF THE SPLEEN

**Tumors.**—Tumors of the spleen are curiously rare. Many primary tumors have been described, but the only ones which deserve mention are hemangioma and lymphangioma. As the spleen plays the part of a filter it might be expected that secondary carcinoma would be very common. On the contrary it is comparatively rare. Almost every organ may be the seat of secondary growths, yet the spleen may remain free. This is in striking contrast to other reticulo-endothelial organs such as the lymph nodes and bone-marrow. Tumor cells are undoubtedly arrested, but they are evidently unable to grow and multiply, so that they die out. The usual site of the primary tumor is the breast, the next most common being the lung.

**Cysts.**—Cysts of the spleen are rare. Primary cysts of unknown origin may occur. Echinococcus cysts are less uncommon in countries where the disease prevails. Hemangioma and lymphangioma may cause cystic formation.

**Atrophy.**—The spleen becomes markedly atrophic in old age, and may be only one-third of the normal weight. Similar atrophy may occur in wasting diseases of long duration. The capsule is thickened and wrinkled, and the cut surface has a markedly fibrosed appearance. The lymphoid tissue disappears, and the pulp is atrophic.

**Perisplenitis.**—Perisplenitis is a rather indefinite term which denotes fibrous thickening of the capsule, sometimes extreme in degree. It is seen in senile atrophy, and in some enlarged spleens the surface is covered with thick fibrous patches. The most extreme thickening is seen in Pick's disease.

**Accessory Spleens.**—Accessory spleens or spleniculi are common. Usually there is only one, sometimes two, but in rare cases several hundred have been present. This is a reversion to the primitive condition in which the splenic tissue is not collected into a definite organ, but is strewn throughout the subserous coat of the gastro-intestinal tract.

## THE LYMPH NODES

The lymph nodes are definite glandular collections of lymphoid tissue, but this tissue is also scattered widely throughout the body in the alimentary canal, liver, spleen, thyroid gland, etc. It follows that general disease of lymphoid tissue will not be confined to the lymph nodes. The nodes do not consist only of lymphoid tissue. They contain reticulo-endothelial cells, and it is by virtue of these cells that the nodes play the part of filters and tend to retain any irritants which may reach them in the lymph stream. The pathology of the lymph nodes is often peculiarly difficult, because they possess a remarkable power of reacting to an irritant by proliferation and hyperplasia of their cells, so that it may be almost impossible to tell if we are dealing with an inflammatory condition or a true neoplasm. It is therefore of the greatest importance that when a practitioner sends an excised lymph node to the pathologist for diagnosis, he should at the same time send all the clinical information available. Too often the specimen is sent in without a word of history. This may be taken as subtle flattery for the omniscient pathologist, but it is actually an expression of culpable carelessness, and is grossly unfair to the patient who has entrusted himself to the practitioner. It may be noted that the inguinal nodes are the least suitable for biopsy (although often chosen for the sake of convenience), because they frequently show evidence of previous infection (from legs and genitalia) in the shape of fibrosis and distortion. The site from which the gland was taken must therefore be stated.

Lymph nodes, like the spleen and thyroid gland, respond to disease by enlargement. There are therefore many causes of lymph node enlargement, but the more important of these may be divided into four main groups: (1) inflammation, (2) chronic granulomas, (3) lymphoblastomas or malignant lymphomas, and (4) secondary tumors.

## INFLAMMATION OF THE LYMPH NODES

**Acute Lymphadenitis.**—This is the result of virulent bacteria (staphylococcus, streptococcus) being arrested in the lymph node. The node

is enlarged, painful, and tender, the cut surface varies from pink to gray, and a milky juice can be scraped from the surface. The *microscopic picture* varies with the severity of the inflammation. If this is suppurative, the sinuses will be crowded with polymorphonuclear leucocytes, and patches of necrosis will be scattered through the gland which eventually is converted into an abscess. It is comparatively seldom that the inflammation proceeds to suppuration. Usually the lesion clears up by resolution, and in such cases there is no necrosis, but merely marked hyperplasia of lymphoid and reticulo-endothelial tissue to which the enlargement of the gland is due. In typhoid fever there is a great proliferation of the endothelial cells lining the sinuses; these are cast off, and may completely fill the lumen of the sinus.

It is the regional lymph nodes which drain an area of acute inflammation that develop acute adenitis. Some of the more important examples are the following: occipital and superficial cervical glands infected from pediculosis and wounds of scalp and ear, deep cervical glands from teeth and mouth, lateral pharyngeal glands from the pharynx with suppuration and the formation of a retropharyngeal abscess, axillary glands from the hands, inguinal glands from the genitals, leg, or foot. In all of these instances there may be a chronic lymphadenitis if the infection is less acute in type.

#### **Chronic Lymphadenitis.**—

Chronic enlargement of a lymph node occurs when the node drains a focus of chronic inflammation. The gland is moderately enlarged, firm and homogenous. *Microscopically* the change is a pro-

liferative rather than an exudative one. There is hyperplasia of the reticulo-endothelial cells, large numbers of the endothelial cells becoming swollen, rounded and cast off into the greatly dilated lymph sinuses, an appearance to which the name of *sinus catarrh* is given. (Fig. 398.) It may be noted in passing that lymphoid structures and hematopoietic structures in general respond to irritation by hyperplasia, so that it may be very difficult to distinguish between inflammatory and neoplastic conditions. This is a matter of supreme importance in connection with the lymphoblastoma group. Chronic lymphadenitis is a very common condition. The cervical

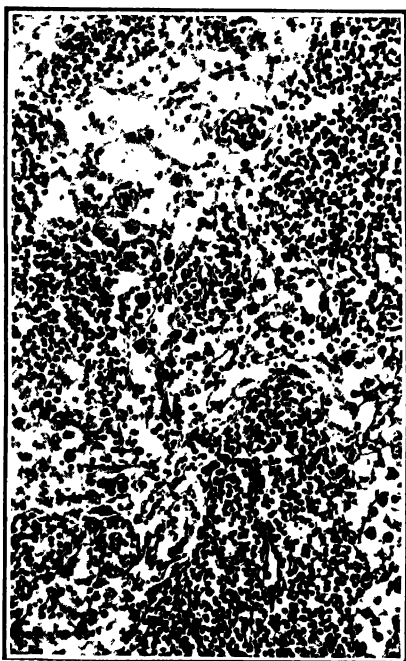


FIG. 398.—Chronic lymphadenitis.  $\times 150$ .

group is most often involved, due to infection from the mouth, tonsils, and teeth. Infection of the leg or the male genitalia will cause enlargement of the inguinal glands; infection in the lung, lesions in the bronchial glands, etc.

**Mesenteric Lymphadenitis.**—In children and young adolescents there sometimes occurs an acute abdominal condition simulating appendicitis, diverticulitis, renal colic, etc., but in which the major finding at operation is inflammatory enlargement of the mesenteric lymph nodes in the ileocecal angle. In only a few cases can bacteria be demonstrated, and these are usually streptococci. Some of the cases are tuberculous. It is difficult to explain how the lesion in the lymph nodes gives rise to the clinical picture. Some of the symptoms may be due to spasm of the bowel.

### CHRONIC GRANULOMAS OF THE LYMPH NODES

**Tuberculosis.**—Tuberculosis is one of the commonest causes of enlargement of lymph nodes. The three groups most commonly involved are the cervical, bronchial, and mesenteric. The first is infected from the mouth and throat, usually the tonsils, the second from the lung, the third from the bowel. Mesenteric lymph node tuberculosis is likely to be caused by drinking tuberculous milk or



FIG. 399.—Tuberculosis of a lymph node showing several large caseous areas in the enlarged node.

swallowing tuberculous sputum. Although theoretically it is possible for the bacilli to pass through the intact wall of the bowel, in practice the more careful the examination the more often will an intestinal lesion be found. When the ileocecal group is involved in children there may be symptoms like those of acute appendicitis, *i. e.*, sudden onset of abdominal pain and rigidity, fever, vomiting, and a moderate leucocytosis. These symptoms are apparently due to spasm of the bowel.

The glands are at first discrete and firm, but when periadenitis occurs they become matted together. The cut surface shows tuberculous areas which are at first gray and translucent, but later become yellow, opaque, and caseous. (Fig. 399.) The entire gland may eventually become caseous and break down, so that a mere shell is left. In this way a cold abscess is formed which discharges on the surface (best seen in the neck), with the establishment of persistent sinuses which finally heal with deep scar formation. It must not be thought that this steady progression is the usual course. As a rule in response to appropriate treatment the condition clears up and does not go on to extensive caseation.

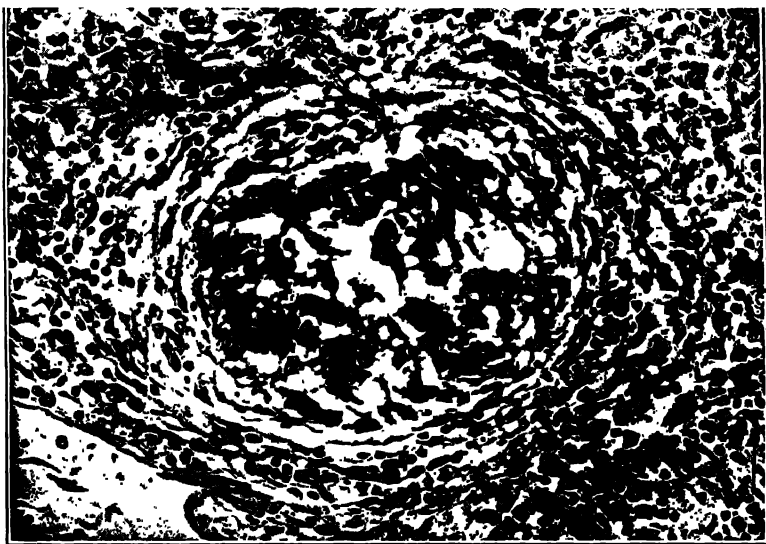


FIG. 400.—A tubercle. Epithelioid cells form the principal part of the tubercle.  $\times 250$ .

The *microscopic picture* shows the usual *tuberculous follicles* composed largely of *epithelioid cells* with a few giant cells. (Fig. 400.) In the caseous cases much of the structure of the node has disappeared. There is no tissue in which it is so hard to find tubercle bacilli; when present they are never numerous; it seems as if they are destroyed in the gland in some way. As healing occurs fibroblasts proliferate and dense collagen fibers are laid down. Calcification is common in the caseous glands, particularly in the bronchial lymph nodes. However quiet the lesion may appear to be, there is always a danger that it may set up another focus elsewhere (bone, adrenal, etc.), by way of the blood stream. Sometimes the lesions are not discrete tubercles, but take the form of a *diffuse hyperplastic tuberculosis*, characterized by reticulo-endothelial hyperplasia and sheets of epithelioid cells, but no caseation and no giant-cell formation. It is more than probable in

the light of recent knowledge that many, perhaps most of these cases are really examples of sarcoidosis.

**Sarcoidosis: Boeck's Sarcoid.**—In several respects the condition about to be described is one of remarkable interest. It was first described by Jonathan Hutchison in 1869, but it has masqueraded under such a variety of names that it is only in recent years that it has come to command general attention. Perhaps the best descriptive name is that of *benign lymphogranuloma*, for clinically the lesions may simulate those of Hodgkin's disease, whilst histologically it may mimic tuberculosis. Sarcoid is certainly a misleading name. There is usually an astonishing absence of symptoms, the disease is not fatal, and autopsy reports are correspondingly rare. The condition appears to be particularly common in Scandinavian countries.

The diversity of lesions, or rather of organs involved, is remarkable. The chief tissues involved are the skin and lymph nodes, both superficial and deep, but there may be splenomegaly, hepatomegaly, and lesions of the lung, myocardium, pancreas, testis, tonsil, bones of the fingers, parotid and lachrymal glands, and uveal tract of the eye. I have seen a sarcoid lesion in the hypothalamus which caused diabetes insipidus, and similar cases have been reported. To make matters more confusing, lesions may be confined to the skin or lymph nodes or bones or the eye. The bone lesions are practically limited to the phalanges of the fingers and toes. The disease lasts for months or years, with a tendency to fibrosis and healing. Healed lesions are represented by scars. In the lungs this scarring is of particular importance, because there can be little doubt that many cases which in the past have been considered as healed military tuberculosis are in reality examples of healed sarcoidosis. There may be quite generalized interstitial pulmonary fibrosis causing dyspnea and cyanosis due to failure of the right ventricle. Radiologically the bones show a peculiar reticulated rarefaction in the early stages; later there are small punched-out areas. There is a remarkable alteration in the plasma proteins, consisting of an unusual increase in the globulin fraction, usually with a pronounced elevation in the total plasma protein. In this respect the disease resembles multiple myeloma, kala-azar and lymphogranuloma venereum, in all of which elevation of the plasma globulin is a distinctive feature.

The *lesions* are rounded circumscribed masses resembling military tubercles, the chief component of which is epithelioid cells, together with macrophages, giant cells, and occasional eosinophils. It may be difficult to decide between sarcoidosis and tuberculosis, particularly in a lymph node, but the peculiarly clean-cut, almost diagrammatic, character of the sarcoid lesions help the observer in his decision. The giant cells are larger than those of tuberculosis and contain more nuclei. (Fig. 401.) There is a striking and characteristic absence of caseation, and there is generally no surrounding lymphocytic infiltration. Fibrosis increases with the age of the lesion. Silver stains show a delicate reticulum which is absent, owing to destruction in tuberculosis.



The lesions are identical with those of *uveoparotid fever* (uveoparotitis) in which there is bilateral painless enlargement of the parotid glands with involvement of the uveal tract. This condition may be regarded as a form of sarcoid due to the same etiological agent.

The *etiology* of sarcoidosis is uncertain, or, if one prefers it, unknown. There are two chief views: (1) it is a chronic granuloma closely resembling tuberculosis histologically but caused by some undiscovered agent; (2) it is an atypical manifestation of tuberculosis. Evidence in favor of the latter view is gradually accumulating (Cameron and Dawson). In many ways the disease resembles chronic miliary tuberculosis. The usual absence of tubercle bacilli may be compared with the absence of streptococci in the lesions of rheumatic fever. Non-caseating bacteria-free lesions might occur in individuals with high immunity and low sensitivity. Tubercle bacilli produce sarcoid lesions in animals like the white rat which have a high natural resistance to tuberculosis. Finally, occasional cases are reported in which tubercle bacilli have been isolated from sarcoid lesions both by culture and animal inoculation.



FIG. 401. —Sarcoidosis.  $\times 160$ .

**Syphilis.**—In a discussion of the differential diagnosis of lymph node enlargement syphilis is often mentioned. It is important to have a clear idea of what is meant when we speak of syphilis of the lymph nodes. The enlargement may occur in the primary, secondary, or tertiary stage. In *primary* syphilis the regional lymph nodes are enlarged and hard. In the usual type of lesion the inguinal glands are involved, but if the chancre is on the lip the submental nodes are enlarged. In the *secondary stage* the glands all over the body are moderately enlarged. In *tertiary* syphilis gummatous formation has been reported but is extremely rare. This is the point to remember in the differential diagnosis, even when the Wassermann reaction is strongly positive. The histology is not characteristic, *i. e.*, a proliferation of epithelioid cells, lymphocytes, and plasma cells. In the primary and secondary forms the demonstration of the *Spirochaeta pallida* is usually easy.

## LYMPHOBLASTOMAS OR MALIGNANT LYMPHOMAS

**Hodgkin's Disease.**—This is a disease of the hemopoietic organs, *i. e.*, bone-marrow, lymph nodes, spleen, and liver. It is invariably fatal. Whether it is inflammatory or neoplastic in character is a matter

of dispute. While studying the features of the disease the reader may weigh in his mind whether they point to an inflammatory or a neoplastic process.

**Symptoms.**—The disease may occur at any age, but is commonest in middle life, usually in men. It is always fatal, but the duration varies greatly. The average case lasts between one and two years, but a very acute form may prove fatal in a few months, while chronic cases may last for years. I know of one case where a patient applied for life insurance sixteen years after a diagnosis of Hodgkin's disease had been made by biopsy independently in two first class laboratories of surgical pathology. In adults Hodgkin's disease is about twice as common as lymphosarcoma, but in children the incidence of the two diseases is about equal. The disease is usually first detected by an enlargement of the cervical glands, first on one side and then on the other, but deep glands (mediastinal, mesenteric) may have been enlarged long before the superficial ones become palpable. The spleen is enlarged to a considerable degree in 75 per cent of cases. The liver shows a slighter degree of enlargement in 50 per cent of the cases. A progressive anemia is constant, but the leucocytes show no uniform change. They may be increased or diminished in numbers, monocytes may be more numerous than normal, and occasionally there is a well-marked eosinophilia. Megakaryocytes have been found in the blood, and the blood platelets are often increased. Fever is common. Often this assumes the so-called Pel-Ebstein type, characterized by spells of mild fever lasting for a few days, and separated by intervals of a week or two of normal temperature. In other cases the fever is more continuous. Less common symptoms, but worthy of mention, are pruritus (itching), which may be present long before the glandular enlargement, pigmentation, and in rare instances infiltration of the skin. There may be dyspnea, cyanosis, paralysis, and other signs of pressure by the enlarged lymph nodes.

**Lesions.**—The affected *lymph nodes* are enlarged, usually in groups. The greatest enlargement may be in the mediastinal, mesenteric, and retroperitoneal groups. The groups are not continuous with one another, thus differing from the usual picture of lymphosarcoma. For long the nodes may remain discrete, but eventually they may become fused as in tuberculosis. Sometimes there may be invasion of the surrounding tissue; thus invasion of the lung may take place from the mediastinal glands. The cut surface is pale gray, homogeneous, translucent, and moist, and has been likened, not inaptly, to fish-flesh. Later it may become yellow owing to necrosis. The *spleen* is large and firm, but it often has not the homogeneous appearance of the lymph nodes, for scattered through it are numerous opaque patches, gray or yellow, like pieces of suet. (Fig. 402.) These represent areas of "Hodgkin tissue," the change having commenced in the lymphoid follicles. Later the process becomes more diffuse. Small gray areas may be seen on the enlarged *liver*; these are lesions confined to the portal tracts. The *bone-marrow* may appear red and hyperplastic. Other organs may more rarely show lesions, *e. g.*, intestine, stomach, kidney, and wherever there happens to be lymphoid tissue. In exceptional cases the disease may be mainly or entirely confined to one organ, so that it is possible to have Hodgkin's disease of the lung, stomach, etc.

The *microscopic appearance* is the same wherever the lesions occur,

but in any one site it may be extremely varied in character. Indeed its pleomorphism is its most characteristic feature. The lesion is

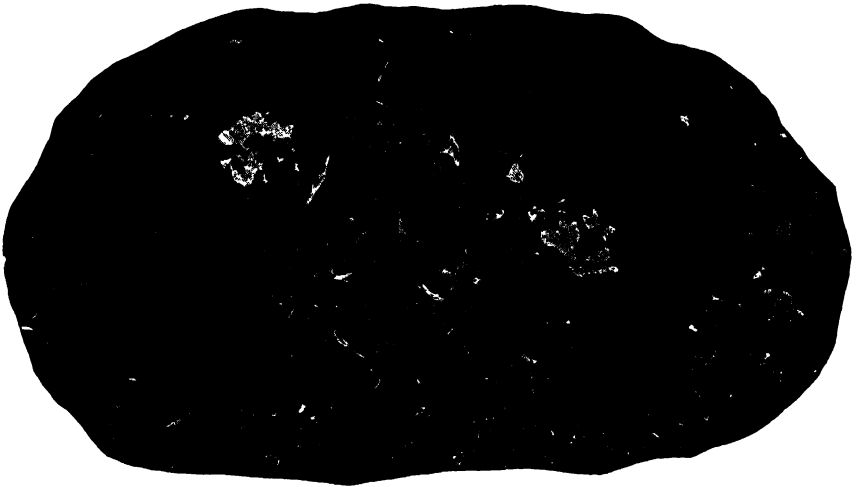


FIG. 402. — Enlarged spleen of Hodgkin's disease showing suct-like areas. (From Boyd's Surgical Pathology.)

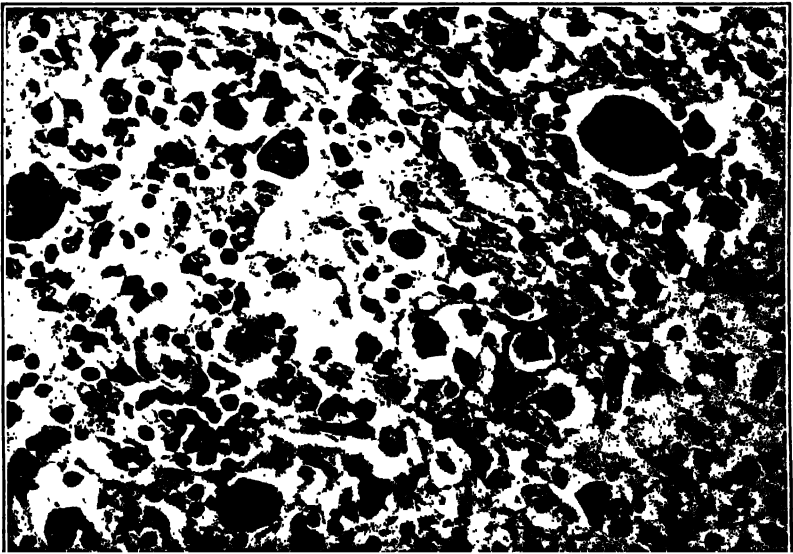


FIG. 403. — Hodgkin's disease. The cytological picture is characteristically pleomorphic. There are several large multinucleated cells of the Dorothy Reed Type.  $\times 350$ .

mainly composed of large pale cells of "epithelioid" type. These large cells are probably derived from the reticulo-endothelial cells of the

node. Even more characteristic is the appearance of very large or giant cells, some of which are mononuclear but many are multinucleated; when the nucleus is single it may be convoluted or ring-shaped. These giant cells are the cells known as the Dorothy Reed or Sternberg cells. (Fig. 403.) The multinucleate forms frequently have two nuclei, one of which is the mirror-image of the other, the so-called "mirror-image giant cell." Lymphocytes, plasma cells, polymorphonuclear leucocytes, and eosinophils may all be present. Eosinophils are particularly characteristic, and help to settle the diagnosis when it is in doubt, but it must not be thought that they are invariably present. Necrosis may appear later, but this is best seen in the spleen. There is a marked and characteristic increase of reticulum shown by silver staining. In the later stages there is dense fibrosis. In the earlier cellular stage the lesion will respond for a time to radiation, but not in the late fibrotic stage. Sometimes there is not the pleomorphism of inflammation but rather the uniform cellular picture of neoplasia. The cells are large, of uniform size, with abundant cytoplasm and the large prominent nucleolus characteristic of malignancy. Mitoses are common. Reticulum formation is at a minimum. The lesion is much more invasive than is the ordinary form. Such cases have been called *Hodgkin's sarcoma*.

Jackson and Parker have analyzed a large series of lymphadenopathies in which Reed-Sternberg cells are present and which may therefore be regarded as Hodgkin's disease. They find that the cases fall into 3 groups, which they call paraganuloma (38 cases), granuloma (237 cases) and sarcoma (51 cases). In the paraganuloma the disease is confined to the cervical lymph nodes although the spleen may also be involved, the capsule remains intact, the principal cell is the lymphocyte, and Reed-Sternberg cells are few and difficult to find; the lesion is easily mistaken for lymphadenitis. The granuloma is the common phase of the disease. Its characteristics and those of the sarcomatous form have already been outlined.

**Nature and Cause.**—The cause of Hodgkin's disease is unknown and even the nature of the condition is uncertain. It has been regarded as: (1) an atypical form of tuberculosis; (2) a specific infective granuloma of unknown origin; (3) a tumor; (4) a transition form between a granuloma and a tumor.

(1) At various times during the past half century the view has been maintained that Hodgkin's disease is a special form of tuberculosis. Ewing, noting the not infrequent association of the two lesions in lymph nodes remarks that "tuberculosis follows Hodgkin's disease like a shadow." The arguments against this view seem more formidable than those in favor of it.

(2) The most reasonable view appears to be that the disease is a specific infective granuloma of unknown origin, in which case the name Hodgkin's granuloma would be justified. The diversified cytological picture, the necrosis, and the subsequent fibrosis are all in favor of this idea. Against it may be set the invariably fatal out-

come, and the regularity in the distribution of the lesions which is not seen in any of the other infective granulomata. It has been suggested that the infective agent is a filterable virus on the ground of Gordon's demonstration that injection of a suspension of Hodgkin's lymph nodes into the brain of a rabbit produces a fatal encephalitis, and that stained films of the gland suspensions show minute spherical "elementary bodies" like those of vaccinia virus. Later, however, it was shown that normal human bone-marrow contains an agent which will produce encephalitis in the rabbit (Friedemann), and that the Gordon reaction depends on the presence of eosinophils in the diseased tissue (Turner *et al.*). Forbus and his associates have isolated *Brucella melitensis* from the lymph nodes, and by inoculating animals with the strains isolated they have produced granulomatous lesions of the lymphoid structures bearing some resemblance to those of Hodgkin's disease. They do not claim that *Brucella* is the cause of the disease. Lesions suggestive of Hodgkin's disease have been described in a number of domestic animals, particularly in swine by Forbus and Davis, but in no instance can these be regarded as identical with those of the disease as seen in man.

(3) The neoplastic theory is the most popular one at the present time. The chief points in its favor are the invariably fatal course and the resemblance to such an undoubtedly malignant condition as lymphosarcoma. The cytological picture is not that of cancer.

(4) The view that Hodgkin's disease occupies a position between the infective granulomata and tumors, as suggested by Symmers and others, offers an escape from an impasse. Without wishing too much to sit on the fence it may be said that the disease partakes of the characters of both of these conditions. The pleomorphism of the microscopic picture suggests an inflammatory lesion, whereas its local spread and its uniformly fatal termination are characteristic of malignancy.

**The Relation of Symptoms to Lesions.**—It is easy to correlate such symptoms as dyspnea and cyanosis with pressure of enlarged lymph glands in the neck or mediastinum. The glandular masses may press on the spinal nerves as they issue from the canal causing pain, paralysis, etc., or masses may be found lying within the spinal canal and pressing directly on the cord. The enlarged spleen will cause a sensation of abdominal fulness or heaviness. The anemia is due to involvement of the bone-marrow, and the variations in the blood picture (eosinophilia, etc.) may be attributed to the same cause. The cause of the fever is uncertain. If the disease is due to a bacterial infection it is readily explained. If not, the periodic or continuous fever may be connected with the necrosis which is so frequently present.

**Histiocytic Medullary Reticulosis.**—In any series of cases of Hodgkin's disease there will be some which the pathologist is forced to call "atypical." It may well be that future observations may establish some of these cases as separate entities. Scott and Robb-Smith have distinguished one such group and named it histiocytic medullary reticulosis. The reticuloses form a group of diseases characterized by progressive cellular hyperplasia throughout the hemopoietic and lymphatic tissues, and in the example under consideration there is proliferation of histiocytes in the medulla of lymph nodes.

The lymph nodes show a generalized moderate enlargement, the spleen may

be considerably or even greatly enlarged, the liver is slightly enlarged, and the marrow of the long bones red and hemorrhagic. Microscopically there is cellular proliferation in the medulla of the lymph nodes and spleen, the periportal tissue, and the bone-marrow. The medullary proliferation is composed principally of phagocytic histiocytes containing red blood cells and nuclear debris, and non-phagocytic prohistiocytes, large cells with irregular outline and dark nuclei, often showing mitotic figures; there may be giant prohistiocytes, but their dark and twisted nuclei are in sharp contrast to the pale "mirror-image" nucleus of the Dorothy Reed cell of Hodgkin's disease.

The principal clinical features are fever, wasting, generalized lymph node enlargement, together with enlargement of the liver and spleen, and in the final stages jaundice, purpura and anemia with profound leukopenia.

**Lymphosarcoma.**—Hodgkin's disease was first described a hundred years ago, but it was not until 1893 that Kundrat separated the condition known as lymphosarcoma from the general group of the lymphomas. The characteristic feature which serves to distinguish it from Hodgkin's disease is the fact that it arises in one group of lymph nodes or in one collection of lymphoid tissue and spreads to other groups of nodes apparently by way of the lymphatics. The spread tends to be continuous, whereas in Hodgkin's disease it is discontinuous. It may be easier for the clinician to make the distinction than for the pathologist who sees the end stage of widespread involvement in the autopsy room. In addition to the nodes there may be widespread involvement of the lymphoid tissue in the pharynx (tonsils, etc.), gastro-intestinal canal, spleen, bone-marrow, liver and other organs. Many of the other features of Hodgkin's disease may also be present. The spleen may be enlarged, although splenomegaly is not nearly so frequent as in Hodgkin's disease, fever is a common complication, and changes in the blood point to involvement of the bone-marrow. The most constant of these changes is a progressive secondary anemia, but there may be a relative or absolute lymphocytosis. Many cases are undoubtedly examples of aleukemic leukemia which have been unrecognized. It is often not realized by the physician that examination of a blood smear is more valuable than a biopsy. Pure classical lymphosarcoma of the type described by Kundrat is probably a rare disease.

The *gross appearance* of the lesions is very similar to that of Hodgkin's disease, but in lymphosarcoma there is a greater tendency to rupture of the capsule of the glands with invasion and destruction of the surrounding tissues. On the other hand, there is much less necrosis within the tumor, so that yellow patches are not seen. The lymphoid tissue of the bowel may be much swollen so as to form nodular masses on the inner surface. The abdominal and thoracic cavities may be filled with tumor masses of remarkable size considering the state of the superficial nodes (Fig. 404) and there may be extensive infiltration of the lungs.

The *microscopic appearance* shows complete replacement of the mature lymphocytes by much larger hyperchromatic cells with a small amount of basophilic cytoplasm and a round or oval nucleus with a fairly prominent nucleolus; mitoses may be present, but are not easy to recognize. The uniformity of cell type is an outstanding

feature in comparison with the multiplicity of cell forms seen in Hodgkin's disease. (Fig. 405.) There is no increase in reticulum as shown by silver stains. Those reticulum fibers which are present represent the original content of the node, and these are dispersed by the infiltration of neoplastic cells, so that in a given field they appear to be decreased in number. (Fig. 406.)

In some cases there is a generalized lymph node enlargement rather than a neoplasia commencing in one region and gradually extending and becoming disseminated. In these cases the normal architecture is replaced by mature lymphocytes, and the picture is indistinguishable from that of lymphatic leukemia; only a blood examination can differentiate the two lesions. Such a condition may be called *lymphocytoma*; it may terminate as a lymphatic leukemia.

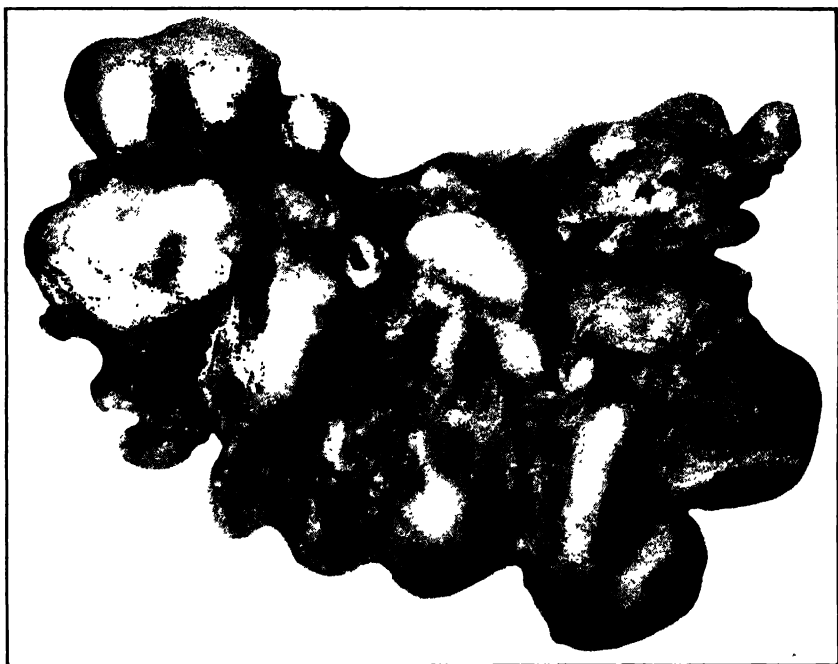


FIG. 404.—Lymphosarcoma. Mass of enlarged abdominal lymph nodes.

**Reticulum-cell Sarcoma.**—This tumor is commonly regarded as a form of lymphosarcoma under the name reticulum-cell lymphosarcoma. This is permissible in regard to tumors of lymph nodes, where the tumor arises from the reticular cells of the node. It may occur, however, in many other situations, including bone, where it forms one variety of bone sarcoma, so that it is better to speak of it as reticulum-cell sarcoma. It is a highly malignant disease, the average duration being less than two years. Although behaving like lymphosarcoma,



FIG. 405.—Lymphosarcoma. There is great uniformity of cell type.  $\times 650$ .



FIG. 406.—Lymphosarcoma; reticulum stain.  $\times 510$



FIG. 407. — Reticulum-cell sarcoma. Compare the size and form of the cells with those in Figure 399.  $\times 650$ .



FIG. 408. —Reticulum-cell sarcoma; reticulum stain.  $\times 510$ .



it may occasionally occur as an isolated lesion, radical removal of which may result in apparent cure. Reticulum-cell sarcoma is a much commoner lesion of lymph nodes than pure lymphosarcoma.

The *macroscopic appearance* is characteristic, but this is only true if the material is properly fixed, so as to prevent distortion by shrinkage, and suitably stained. The cytoplasm of the reticulum cell is usually abundant and faintly acidophilic. (Fig. 407.) The nucleus is double the size of that of a lymphocyte, and is commonly infolded, giving it a reniform appearance. Highly characteristic in well-fixed material is the presence of pseudopod-like processes of both cytoplasm and nucleus, indicating amoeboid activity in the living cell. The tumor cells may often be seen infiltrating the vein walls and almost closing the lumen. The pathognomonic feature is the distribution of reticulum the fibers show an intimate relationship to the tumor cells, encircling groups of cells and sending fibrils between and around individual cells. (Fig. 408.)

**Interrelationship.**—Although in typical cases there appears to be a sharp line of distinction between Hodgkin's disease, lymphosarcoma and reticulum-cell sarcoma, one of these conditions may blend with another. Thus biopsy may show one type, but subsequent autopsy may show another or more than one. Herbut and his associates believe that there are two chemical substances, one of which stimulates proliferation of the myeloid cells and the other the lymphoid cells. In Hodgkin's disease they occur in the urine in nearly equal proportions. The three diseases may arise from a common stem-cell, the reticulum cell.

**Giant-follicle Lymphoma.**—There is a small group of cases which deserve to be separated from the general group of lymphosarcoma. The lesions may remain localized for a considerable time, and the disease is characterized by its prolonged duration of many years and by the marked sensitivity of the lesions to radiation. It has a tendency, however, to terminate as lymphosarcoma or reticulum-cell sarcoma. Both spleen and lymph nodes are involved, and the microscopic picture is one of extreme hyperplasia of the lymphoblastic cells of the germinal centers of the lymph follicles, so that the condition has been called follicular lymphoblastoma (Baehr and Klemperer). It is also known as Brill's disease, but this term is already used for a variety of typhus fever.

**Benign Lymphoma.**—This is an innocent tumor of a lymph node or group of nodes. It is very uncommon, and it is never safe to make the diagnosis from the microscopic picture alone, since this may be identical with that of lymphosarcoma. Indeed in all of these conditions the pathologist should be supplied with all the information possible before making a diagnosis. But if an enlarged gland or cluster of glands in the neck or groin increases slowly in size or remains stationary for a number of years without evidence of involvement of the rest of the lymphatic system, and if this gland when removed shows a replacement of the normal structure by a diffuse arrangement of small round cells such as is seen in lymphosarcoma, the blood meanwhile remaining normal, then it seems justifiable to make a diagnosis of benign lymphoma.

**Leukemia.**—The morbid anatomy of leukemia as well as the blood changes are considered in Chapter XXX, but it is convenient to

mention the condition of the lymph nodes in this place. In the lymphatic form of leukemia there is a general enlargement of the lymph nodes. Sometimes this is almost confined to the deep nodes in the thorax and abdomen so that the superficial glands may show little change. The *microscopic picture* is the same as that of lymphosarcoma, for the nodes are so crowded with lymphocytes that all normal structure disappears. Lymph node enlargement does not form an essential part of the myelogenous form of leukemia, but it may occur, owing to the newly-formed primitive leucocytes (myelocytes) being detained in the sinuses of the nodes or possibly to a local formation by a process of myeloid metaplasia.

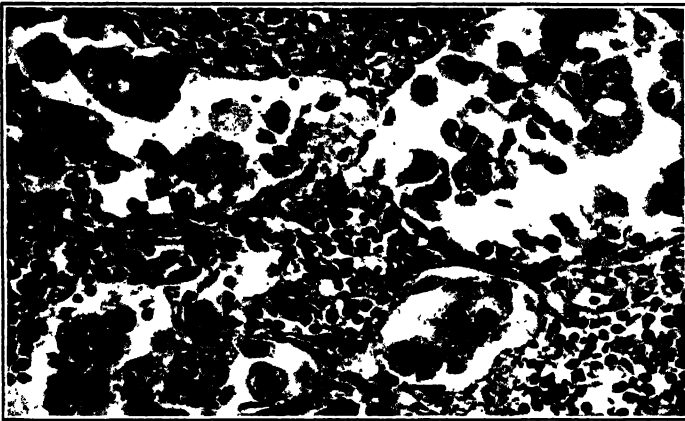


FIG. 409. - Secondary carcinoma of a lymph node. The lymph sinuses are distended by carcinoma cells.

**Infectious Mononucleosis.**—This essentially benign condition, known also as glandular fever, bears some superficial resemblance to the group of diseases which has just been discussed. It is characterized by a mild degree of fever in young persons lasting for two or three weeks, a very sore throat, slight enlargement of the cervical lymph nodes and sometimes the axillary and inguinal groups, moderate enlargement of the spleen, and an increase in the mononuclear cells of the blood. The spleen is moderately enlarged in about 50 per cent of cases. The disease is never fatal, unless spontaneous rupture of the spleen occurs, a remarkable complication which has been reported not infrequently. Necrotic lesions are found in the liver not unlike those of infectious hepatitis, suggesting the possibility of a virus infection and explaining the mild jaundice which sometimes occurs. In addition, many of the organs may show leukemic-like infiltration by mononuclear cells similar to those which dominate the blood picture. The total leucocyte count rarely exceeds 20,000, but the percentage of mononuclears may be from 50 to 95 per cent of the total count, so that at first a distinction from lymphatic leukemia may be impossible. The increase may be in small lymphocytes or in large mononuclears, and it is possible that these may be monocytes rather than lymphocytes. The lymph nodes show lymphoid hyperplasia, but traces of the normal architecture still remain. The condition is apparently due to bacterial infection through the tonsils or the upper respiratory tract, as a result of which lymphoid tissue is unduly stimulated, many of the newly-formed cells appearing in the blood stream.

The blood contains heterophile antibodies, *i. e.*, the serum will clump sheep's red cells even in high dilution (Paul-Bunnell test). This is a useful test in doubtful cases, but it is by no means specific, for it may be negative in infectious mononucleosis and positive in virus pneumonia.

**Secondary Tumors.**—A carcinoma tends to metastasize to the regional lymph nodes. The cancer cells are first found in the peripheral lymph sinus and then in the medullary sinuses. (Fig. 409.) As the tumor cells grow they destroy the lymphoid tissue, until finally the entire node is a mass of carcinoma. The secondary growth may be more or less differentiated than the primary tumor. When the tumor cells break through the capsule the gland becomes firmly adherent to the surrounding tissues, being then inoperable. Malignant melanomas, being epithelial in origin, also metastasize to the lymph nodes, but sarcomas rarely do, spreading as a rule by the blood stream.

## THE RETICULO-ENDOTHELIAL SYSTEM

**Distribution.**—It has been known for many years that if a vital dye, such as trypan blue or pyrrhol blue, is injected into a living animal certain cells take up the dye while others do not (Goldmann). In 1913 Aschoff and Landau introduced the idea of a reticulo-endothelial system to include all those cells which when living were capable of taking up a vital dye and were therefore phagocytic in nature. These cells may be divided into three great groups: (1) reticulo-endothelial cells proper, (2) histiocytes, and (3) monocytes.

(1) The *reticulo-endothelial cells proper* are found in the hemopoietic organs, *i. e.*, bone-marrow, lymph nodes, spleen, and liver. Specialized endothelial cells line the blood and lymph sinuses of these organs, in the liver forming the Kupffer cells which line the sinusoids. All of these cells are very highly phagocytic, they readily detain foreign particles passing through the organ, and they take up vital dyes, India-ink, etc., during life. Beautiful colored illustrations of this process will be found in Cappell's paper. The ordinary endothelial cells lining the vessels are quite unaffected by these methods. Thus when India-ink is injected into the blood stream of a rabbit, the special endothelium of the bone-marrow, spleen, etc., is found to be black with arrested particles, while the ordinary endothelium is untouched. The reticular cells of the splenic pulp, which form the main constituent of the pulp, and similar cells in the lymph nodes are also highly phagocytic. It is possible that the cells of the germinal centers in the nodes belong to this class. There is no proof that the reticular cells bear any relation to the reticulum fibers of lymphoid tissue. (2) The *histiocytes* are the wandering phagocytic cells of the tissue, the adventitial cells of the vessels, etc., which play so prominent a part in inflammation, forming the cells of histogenous origin in that process. They, of course, are found in all organs, not merely those of the hemopoietic series. (3) The *monocytes* are white blood cells derived

from the endothelial elements of the reticulo-endothelial system. They are the important phagocytic cells known by such diverse names as the large mononuclear and transitional leucocytes of Ehrlich, the endothelial leucocytes of Mallory, and the macrophages of Metchnikoff. It is possible that the microglia, which is the source of origin of the phagocytes in the brain and cord, should be included in this far-flung system.

**Function.**—Some of the chief activities of the reticulo-endothelial system are: (1) phagocytosis, (2) storage, (3) antibody formation, and (4) formation of blood cells.

The *phagocytic* power is the most obvious. It is by virtue of these cells that the spleen, lymph nodes, liver, etc., are the great filters of the body. By proliferation they give rise to some of the most actively phagocytic of the inflammatory cells. The *storage power* is manifested toward lipoids, hemoglobin, and iron. When a lipoid such as cholesterol is fed to rabbits for a considerable time the reticulo-endothelial cells become filled with this substance. The intravenous injection of iron is followed by a similar storage. *Antibody formation* is supposed to be carried on by these cells, because when they are "blocked" by India-ink or a vital dye the power of antibody formation is diminished. *Blood formation* is concerned both with white and red cells. The monocytes are formed by proliferation of the special endothelial cells. Erythrocytes are formed in the same way from the endothelium of the intersinusoidal capillaries of the bone-marrow.

**Reaction in Disease.**—The behavior of the reticulo-endothelial system in disease throws light upon its functions during health. (1) The phagocytic function is in evidence in many diseases. The large endothelial phagocytes which constitute the characteristic cytological feature of typhoid fever, the Aschoff cells of rheumatic fever, the cells which fill the sinuses in sinus catarrh of the lymph nodes, the epithelioid and giant cells of tuberculosis, and the "heart failure cells" and "dust cells" of the lungs, are all reticulo-endothelial in origin, many being derived from the tissue histiocytes. The phagocytic power of the reticulo-endothelium enables it to break down red blood cells so that it plays an important part in hemolysis. It is moreover the chief agent in the formation of bilirubin. In hemolytic jaundice removal of the spleen, which is merely a vast collection of reticulo-endothelial cells, will relieve or cure the symptoms. (2) The capacity to store lipoids is demonstrated in a remarkable manner in Gaucher's disease, Niemann-Pick's disease, and Christian's disease. In Gaucher's disease the reticulo-endothelial cells of the hemopoietic organs and in Niemann-Pick's disease the histiocytes and monocytes in addition are distended with lipoid, so that the entire system stands out as if impregnated with a vital stain. In Christian's syndrome there are localized granulomatous deposits of lipoid. In the lipemia of diabetes there is occasional lipoid storage in the cells of this system. In the congested liver of mitral stenosis the Kupffer cells are loaded with hemosiderin, and are therefore much more readily seen than in a normal liver. (3) It seems

probable that there may be a tumor formation of the reticulo-endothelial system. Reticulum-cell sarcoma is the best example. Possibly Hodgkin's disease may belong to this group; if not a tumor it is certainly a disorder of this system of cells, a reticulo-endotheliosis.

## THE THYMUS GLAND

The thymus is partly epithelial and partly lymphoid in structure. At first it is entirely epithelial, being derived from the third branchial cleft, but later in embryonic life it becomes invaded with lymphocytes. The epithelium persists as the Hassall's corpuscles and the cells of the reticulum. The cytotreticulum is derived from the endodermal third branchial pouch, the Hassall corpuscles from the ectodermal cervical sinus.

The thymus is an endocrine gland as well as a lymphoid structure. Rowntree has shown that it has a remarkable stimulating effect on the growth of the young animal, growth that is physical, psychical and sexual. It is a speeding-up process. When full growth is attained the process stops, so that the animal does not become a giant; in this respect the thymus differs from the pituitary. The unique and inexplicable feature is that thymus extract produces almost no effect on the first generation, but if the administration is continued to successive generations, the full effect becomes evident in the third and later generations. If the administration be interrupted for one generation, the cumulative effect of previous administrations is completely nullified.

The size of the thymus is its most important feature. No idea of the size during life can be obtained unless the patient has died suddenly, for the gland undergoes a rapid and remarkable shrinking as the result of infection, starvation, and other hostile influences; this shrinkage takes place at the expense of the lymphocytes. In emaciated children the gland may weigh only 2 or 3 grams instead of the normal 15 or 20 grams. It follows that in cases of sudden death, whether in the child or adult, the thymus may appear to be abnormally large. The average weight at birth is 13 grams, and this gradually increases until at puberty it weighs 35 grams or more. After that period there is a gradual atrophy. The following weights given by Hammar for different periods of life may be useful for reference. At birth, 13 grams; 1 to 5 years, 23 grams; 6 to 10 years, 26 grams; 11 to 15 years, 37 grams; 16 to 20 years, 25 grams; 21 to 25 years, 25 grams; 26 to 35 years, 20 grams; 36 to 45 years, 16 grams; 46 to 55 years, 13 grams. The fall in weight after puberty suggests that the thymus exerts some influence on genital development.

*Hyperplasia* of the thymus is a constant feature of Graves' disease, where it forms part of a general thymico-lymphatic hyperplasia. There is said to be hyperplasia in Addison's disease, acromegaly, castration, myasthenia gravis, and after thyroid feeding.

## STATUS THYMICO-LYMPHATICUS

In cases of sudden death from no obvious cause the thymus and the lymphoid tissue throughout the body may be found to be enlarged, and it is the custom to attribute death in these cases, especially when there is a coroner's inquest, to "status lymphaticus" or "enlarged thymus." There is a remarkable difference of opinion at the present day regarding the importance and even the existence of status lymphaticus. Marine, Warthin, and others describe the condition as a constitutional defect associated with lowered resistance and characterized by hyperplasia of the thymus, lymph nodes and lymphoid tissue

in general, together with under-development of the adrenals, gonads, and cardiovascular system. Greenwood and Woods, on the other hand, after a most careful statistical investigation describe status thymico-lymphaticus as a good example of the growth of medical mythology, in which a nucleus of truth is buried beneath a pile of intellectual rubbish, conjecture, bad observations, and rash generalization, and that it is as accurate to attribute the cause of death to "an act of God" as to status lymphaticus. The most recent report is that of the special committee of the Medical Research Council and the Pathological Society of Great Britain and Ireland (Young and Turnbull) which concludes with the statement that the facts elicited "afford no evidence that so-called 'status thymico-lymphaticus' has any existence as a pathological entity."

The writer has not had sufficient experience with cases of sudden death to enable him to express an opinion on this difficult matter. Two facts, however, must be admitted. The first is that certain persons have an abnormally low resistance to drugs, anesthetics, vaccines, serums, and such poisons as arsphenamine and cocaine. In such persons death may follow the most trivial of causes, such as extraction of a tooth, tonsillectomy, a slight blow, or taking a cold bath. The second fact is that in some persons there is a remarkable lymphoid hyperplasia affecting the lymphoid tissue of the throat, nasopharynx, intestinal canal, lymph nodes, and frequently the thymus, associated with hypoplasia of the adrenals, heart, and great vessels. It has been shown experimentally that removal of the adrenals lowers the resistance of rats to morphine as much as 400 times. The question to be decided is, has this lymphatic constitution anything to do with lowered constitutional resistance? There is no doubt that the diagnosis of status lymphaticus or enlarged thymus has been much misused at coroners' inquests, but on the other hand there does appear to be some relationship between lowered constitutional resistance to certain otherwise trivial injuries and a condition of lymphatic hyperplasia. I may quote the following case from the medico-legal practice of my colleague Dr. Erb, which is surely sufficient proof that the concept of death from status lymphaticus is not a pure myth. One of a group of children who were playing on the road was struck down by a motor car and injured. He did not die, but a little lad watching the accident from an adjoining lawn fell dead. At postmortem the child was found to have an enlarged thymus, a thin-walled hypoplastic aorta, and marked hyperplasia of the lymphoid tissue throughout the body. The cause of death in these cases is quite obscure. The immediate cause is stoppage of the heart, which may be attributed to vagal stimulation. Pressure of a much enlarged thymus on the trachea in children has been known to produce dyspnea, but such pressure has nothing to do with the actual death. There seems to be no justification for the term thymic death, for there is no proof that the thymus has anything to do with the stoppage of the heart.

**Sudden Death.**—A brief note may be allowed here on the subject of sudden death, *i. e.*, death occurring unexpectedly in the course of a few minutes. When called upon to perform an autopsy on such a case it is well to bear seven possibilities in mind: (1) cardiac, (2) pulmonary, (3) abdominal hemorrhage, (4) cerebral hemorrhage, (5) traumatic shock, (6) poisons, and (7) status lymphaticus. Sudden *cardiac* death is discussed elsewhere (page 379). It includes coronary thrombosis, coronary occlusion by atheroma causing sudden myocardial failure, syphilitic aortitis, and rupture of the heart or of an aortic aneurism. Sudden *pulmonary* death may be caused by pulmonary embolism, edema of the glottis, laryngeal diphtheria, and foreign bodies in the pharynx and larynx. Spasm of the glottis is a frequent cause of asphyxia in drowning. In children inhalation of stomach contents may cause fatal spasm of the glottis. The rare cases of death from anaphylaxis may be placed in this group. Fatal *abdominal hemorrhage* may occur into the stomach from a gastric ulcer or a varicose vein at the lower end of the esophagus, or into the adrenals especially in children. In the latter case death is due to acute adrenal insufficiency rather than to loss of blood. Ruptured tubal pregnancy and ruptured abdominal aneurism may be included here. *Cerebral hemorrhage* may be rapidly fatal if massive enough (into the ventricles or a cerebral tumor) or if into a vital center (medulla). Sudden death may occasionally follow epileptiform seizures. *Traumatic shock* may cause death at once or after a few minutes; the heart stops beating. *Poisons* must be borne in mind if no cause of death can be found. The odor of the gastric contents may indicate acute alcoholism or prussic acid (smell of bitter almonds). The contents of the stomach should be placed in a jar and sealed. *Status lymphaticus* has already been considered. Of these varied causes by far the commonest are trauma and cardiac failure. It is they which are likely to result in really sudden death. The others (hemorrhage, etc.) are more apt to bring about death in the course of some hours. In one group of cases of *instantaneous* death, *i. e.*, death in a matter of seconds, not minutes or hours, no lesions may be found in vital organs other than those which in other persons are compatible with good functional capacity. Such cases are probably examples of fatal syncope due to increased irritability of nerve endings and hyperactivity of the reflexes, a physiological state which may be caused by transient undetectable factors (chemical, emotional, etc.) as well as by organic lesions (Weiss).

### TUMORS OF THE THYMUS GLAND

The only tumor which need be mentioned is the *malignant thymoma*. This constitutes one variety of mediastinal tumor and is commonly taken for a lymphosarcoma. It is highly malignant, compresses the trachea and other structures, invades the lungs, and metastasizes to bronchial, cervical and axillary glands, and sometimes to distant organs. The structure varies, and this is natural, because the thymus arises from two cell systems, the one lymphoid and the other epithelial. The usual type of picture is lymphosarcomatous, but occasionally it is frankly carcinomatous. It seems probable

that these two types arise from one or other of the two cell systems. Tumors of the thymus are occasionally present in myasthenia gravis. This has suggested the removal of the thymus, whether or not a tumor is present, in the treatment of this condition, a procedure which has met with marked success.

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## CHAPTER XXX

### THE BLOOD

#### THE BONE-MARROW

THE cells of the blood in extra-uterine life are formed in the bone-marrow. It is only the red marrow which is blood-forming, the yellow marrow consisting of nothing but fat. In the adult the red marrow is confined to the flat bones, *i. e.*, vertebræ, sternum, ribs, skull, pelvic bones. In the child, on the other hand, all the bones are filled with red marrow. About the seventh year microscopic evidence can be detected of a change from the red to the yellow marrow, the change being evident to the naked eye at the fourteenth year, and by the twenty-first year all the red marrow of the long bones has become replaced by fat and is therefore of the yellow type. The change first appears in the distal bones and is always most complete in them. A little red marrow is left in the proximal bones, and at the proximal end of these bones, *i. e.*, at the upper end of the femur and humerus. When functional hyperplasia of the marrow occurs, it first becomes apparent in the proximal bones and only later involves the distal bones. The marrow of the femur is often red when that of the tibia is still yellow. Red marrow is much more vascular than yellow marrow. It is natural, therefore, that secondary carcinoma should be more common in the humerus and femur than in the bones of the forearm or the tibia.

It is easy to describe the *cells* which may occur in red marrow, but it is not so easy to recognize them under the microscope. Far the most numerous cells are the myelocytes, followed by the normoblasts. There are three times as many white as red cells. Myeloblasts and megaloblasts are rarely seen in normal marrow. The myelocytes can be recognized by the granules in the cytoplasm. The normoblasts are smaller, and present a "drop of ink" appearance, the intensely dark nucleus having so little of the characteristic red cytoplasm around it that it may be impossible to detect the latter, so that the cell may be mistaken for a lymphocyte. It is safe to say that nearly all lymphoid-like cells in the marrow are normoblasts. In health multiplication takes place at the normoblastic level and megaloblasts are seldom seen.

The large megakaryocyte with its basket-work nucleus and the polymorphonuclear leucocytes are easily recognized. The best studies of marrow cells are made on smears of marrow obtained by sternal puncture during life. Within three hours after death the marrow presents a distorted picture, and even after one hour the cell staining is not as good as during life.

The bone-marrow readily undergoes *functional hyperplasia*, as a result of which a very extensive actively functioning tissue is formed. The chief evidence of hyperplastic activity is the conversion of the yellow marrow into the red variety. The bony trabeculae of the yellow marrow become absorbed, and if the hyperplasia is marked there may be absorption of the compact bone so that the medullary canal is widened. First the proximal and then the distal bones become filled with red marrow. If the marrow of the femur is examined routinely at autopsy the observer will be surprised to find how often it is red instead of yellow owing to the presence of terminal infections, etc. The two chief causes of functional hyperplasia are anemia and infection; in the first the response is mainly erythroblastic, in the second it is mainly leucoblastic, but pure forms of the reaction are seldom seen. In the leucoblastic reaction the new cells are mainly myelocytes. In the erythroblastic reaction they may be either normoblasts or megaloblasts. The former are characteristic of secondary anemia, the latter of pernicious anemia. As already mentioned, it is easier to describe the types of reaction than to recognize the individual cells under the microscope.

**The Bone-marrow in Blood Diseases.**—The marrow must be considered in every disease of the blood. It will usually show some change. This change may be primary as in pernicious anemia and leukemia, or it may be secondary as in secondary anemia. Instead of describing these changes here it will be more convenient to take them up when the individual diseases are considered.

## THE ANEMIAS

Anemia is a condition of the blood in which the concentration of hemoglobin is below normal. This may be brought about in two ways: there may be excessive loss of blood either from hemorrhage or hemolysis (hemorrhagic and hemolytic anemias); there may be deficient blood formation (deficiency anemias). (1) In anemia due to acute hemorrhage the cells and hemoglobin are reduced equally; it is a normocytic and normochromic anemia. In chronic hemorrhage the picture is that of an iron deficiency anemia with low color index (hypochromia). When anemia is due to hemolysis the icterus index is high and the number of reticulocytes is increased. (2) The normal growth of red cells requires non-specific building stones and also certain specific principles. The *building stones* may not be manufactured properly because of the action of toxins, cachectic conditions, etc., on the marrow or because of primary deficiency and atrophy of the marrow. The *specific principles* are iron and the antianemic principle of the liver. Iron is necessary for normal maturation at the normoblastic level and the filling of the red cells with hemoglobin. There may be too little iron in the food, it may be poorly absorbed, or it may be lost from the body (chronic hemorrhage). The result is a hypochromic microcytic anemia in which the cells are not much reduced

in number but are small and have too little hemoglobin; the anemia responds to iron. The antianemic principle of the liver is necessary for the maturation of megaloblasts. It is formed in the stomach by the action of an intrinsic factor in the gastric secretion on an extrinsic factor in the diet. The gastric factor (intrinsic) may be lacking, the result being pernicious anemia; or the food factor (extrinsic) may be lacking, the result being the tropical nutritional anemias; or the antianemic principle may not be properly absorbed (due to intestinal disease) or stored in the liver (due to cirrhosis, etc.). In all these cases there is a macrocytic hyperchromic anemia, which responds well to liver.

From the above summary the causes of the anemias may be classified as follows: (A) *Increased blood loss*: (1) hemorrhage, (2) hemolysis. (B) *Decreased blood formation*: (1) Deficiency of specific substances: (a) iron, (b) antianemic principle or the factors which create it. (2) Depression of marrow function (aplasia): (a) nephritis, toxemias, cachexias; (b) idiopathic aplastic anemia. The various anemias will be considered under the headings of Deficiency, Hemolytic and Aplastic Anemias together with a note on Secondary Anemia.

### THE DEFICIENCY ANEMIAS

Of late years it has become increasingly evident that a number of the anemias have a nutritional basis. These are the nutritional or deficiency anemias. The group comprises pernicious anemia, chlorosis and idiopathic hypochromic anemia, to which may be added the anemia of sprue, coeliac disease, and possibly other forms of anemia. Some element necessary for blood formation may be lacking in the diet, or the body may be unable to utilize it even though it is present.

**Pernicious Anemia.**—The form of anemia commonly called pernicious was first described by Addison, so that it is sometimes known as Addison's anemia, a more appropriate term than pernicious anemia, as the disease is no longer "pernicious" since the introduction of liver therapy. But old names in medicine are hard to displace.

**Clinical Features.**—The disease is usually one of middle age, affecting the two sexes equally, although occurring at an earlier age in women. The symptoms are those of a gradually progressive anemia. As Addison remarked in his original contribution: "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of the languor which is shortly to become so extreme." The course is marked by very remarkable intermissions during which the symptoms clear up and the blood returns toward the normal. In exceptional cases the red cell count may rise from 1,000,000 to 3,000,000 in the course of two or three weeks without any treatment whatever. Before the introduction of liver therapy the course was progressive and uniformly ended fatally, but varied extremely in its degree of acuteness. The symptoms are those of any severe anemia, *i. e.*, pallor, shortness of breath, palpitation, edema. But there are

two features which are characteristic of the pernicious form of anemia; these are achlorhydria and spinal cord symptoms.

The *achlorhydria* is often spoken of as *achylia gastrica*. The two terms are not synonymous, for the latter indicates suppression of all the elements of the gastric juice—pepsin and rennin as well as hydrochloric acid. This suppression often occurs in pernicious anemia, but it is not so constant as achlorhydria. It is a complete achlorhydria, whereas that of carcinoma of the stomach is never constantly complete. It is probable that the achlorhydria antedates the development of the anemia by a considerable period. Often associated with it is loss of appetite (*anorexia*), which may cause a wrong diagnosis of cancer of the stomach. *Spinal cord symptoms* appear in about 5 per cent of the cases, and take the form of ataxia, sensory disturbances, spasticity, and loss of vibration sense in the bones of the leg. The symptoms bear no relation to the severity of the blood changes nor even to their presence, for they may develop before the appearance of any alteration in the blood. In addition to spinal cord symptoms minor nervous symptoms are very common, occurring in about 80 per cent of the cases. They take the form of numbness, tingling, and paresthesias in the arms and legs. These common symptoms are not related to cord lesions, being due to a mild peripheral neuritis.

**Blood Changes.**—The blood picture varies greatly with the stage of the disease, being very abnormal during an exacerbation but often showing little change during an intermission. The changes described below are those of a severe relapse. All the formed elements of the blood are diminished in number, the red cells, the leucocytes, and the platelets. In severe cases the *red cells* may only number 1,000,000 or less. Any anemia in which the red cell count is below 2,000,000 is probably, but not necessarily, pernicious in type. In remissions the count may be as high as 4,000,000. The hemoglobin is also diminished but not in proportion, so that the *color index* (ratio of hemoglobin percentage to percentage of red cells) is high and may be above 1, even as high as 1.5. The red cells, at least many of them, are well colored; they are hyperchromic, in striking contrast to the condition in the hypochromic or achromic forms of anemia. (Plate XXIV, *B*.) More important than the number of red cells in the presence of qualitative changes. Just as the characteristic lesion of pernicious anemia is a megaloblastic reaction in the bone-marrow, so the characteristic change in the blood is a megalocytic or macrocytic anemia. The large *macrocytes* can be seen readily in a stained film, but more important than the presence of occasional large cells is the fact that the *average* size of the red cells is above normal. The average diameter of normal red cells is 7.5 microns, while the average in pernicious anemia may be as high as 8.5 microns (Price-Jones). Pernicious anemia belongs to the megaloblastic and macrocytic group of anemias. The variation in size, which normally is from 6 to 9 microns, in pernicious anemia may be from 4 to 12 microns. Many of the red cells are therefore smaller than normal. These are called *microcytes*, and the variation

is known as *anisocytosis*. The large cells are hyperchromic, but the microcytes are hypochromic. *Poikilocytosis* (*poikilos*, manifold) may be marked, the cells varying greatly in shape, many being tailed or shaped like a cocked hat.

The tendency in pernicious anemia is for the red cells to revert to a more primitive or embryonic type, for the essence of the disease is a failure on the part of the red cells of the marrow to mature sufficiently quickly. The megaloblastic reaction of the marrow and the macrocytic type of anemia are evidence of this tendency. Many of the cells show *polychromatophilia*, the cytoplasm being of a slaty color owing to having taken up both the red and blue stain. This is most marked in the megaloblasts. The cytoplasm of the original red cell is entirely basophilic. It becomes partly acidophilic as hemoglobin

begins to appear, and at this stage shows polychromatophilia. It is only when the cell is mature that it becomes completely acidophilic. *Basophilic stippling* (granular degeneration) may be present; it is merely another manifestation of the same basophilic substance, which in this instance takes the form of fine granules staining blue. The presence of *reticulocytes* is an indication of immaturity, for the reticulum is another form of the same basophilic material. In health reticulated red cells form 1 per cent of the total count, but in pernicious anemia they usually form 5 per



FIG. 410. Increase of reticulocytes in pernicious anemia. Four of the red cells show reticulation.  $\times 1400$ .

cent. (Fig. 410.) The best indication of successful activity on the part of the marrow is an increase in the reticulocyte count. There is a marked rise in a remission, and a specially great increase when liver therapy is commenced. In aplastic anemia, where the bone-marrow shows no activity, there is a complete absence of reticulocytes. The reticulation is not shown in an ordinary film; vital staining has to be used.

*Nucleated red cells* provide another indication of immaturity. They may be normoblasts or megaloblasts. The latter are commoner and much more characteristic, as normoblasts may occur in any severe anemia, but megaloblasts are seldom found except in pernicious anemia. The megaloblast is much larger than a normoblast, its nucleus is larger and more open, and the cytoplasm is polychromatophilic or even basophilic. The nucleus may show mitosis. They can always be found if the count is below 2,000,000, but when it is above 2,500,000

it may be difficult to find a single megaloblast. Owing to the immaturity of the red cells in pernicious anemia, their fragility is diminished rather than increased, for it is the older cells which become more fragile when tested with hypotonic salt solution.

The *leucocytes* diminish in number, so that there is a *leucopenia*. This affects chiefly the polymorphonuclears, so that there is a relative lymphocytosis. The polymorphonuclears are much more lobed in pernicious than in other forms of anemia. This is a useful practical point. Indeed it has been said that in studying the anemias more may be learned from looking at the white cells than at the erythrocytes. There is no leucocytosis even in acute infections. The fault lies in the marrow. This is filled with myelocytes, but they fail to mature, so that there is a decrease in the polymorphonuclears. Myelocytes are not infrequently found in the blood. The *platelets* are much diminished in number (thrombocytopenia), and they may disappear altogether. The *plasma* shows a characteristic yellow tinge due to an increased bilirubin content, the result of increased blood destruction. The icterus index is between 5 and 15 (the normal maximum is 5), and there is a positive indirect van den Bergh reaction, with an increase of urobilinogen in the urine. These serological findings are of great value in those difficult cases where the cytological picture is so indeterminate that no definite diagnosis can be made.

**Morbid Anatomy.**—The lesions of pernicious anemia are partly primary in character, but mostly secondary either to the anemia or to increased blood destruction. The two most constant pathological findings are a megaloblastic type of bone-marrow and marked siderosis. The intensity of these lesions will depend on the stage of the disease at the time of death. If the patient dies during an acute exacerbation, the megaloblastic reaction, the siderosis, and all the secondary lesions will be marked, whereas they may be trivial if the patient dies of some intercurrent disease during an intermission. This is not true of lesions of the spinal cord and possibly those of the alimentary tract. It will be seen from the following description that the lesions may be divided into five groups: (1) Those due to the anemia (fatty degeneration, hemorrhages); (2) bone-marrow changes; (3) siderosis, increased phagocytosis by the reticulo-endothelial cells, and other evidences of blood destruction; (4) lesions of the alimentary tract; (5) lesions of the nervous system.

The *skin* is of a lemon-yellow color, and has not the pure pallor of secondary anemia. There is a remarkable absence of wasting, and the abundant fat is also lemon-yellow. The *muscles* are normal or deep red in color. Petechial *hemorrhages* are common in the serous membranes and can be seen during life in the retina. These changes are due to fatty degeneration of the walls of the small vessels. The fatty degeneration is caused by the anemia. The fatty change is best seen in the *heart*, which is pale, very flabby, so that it collapses when held up by the apex, and the wall of the left ventricle and the papillary muscles show a yellow speckling known as the "thrush

breast" or "faded leaf" appearance. (Fig. 169.) This is marked when the anemia is severe, but may be slight or absent if death occurs during a remission. The *liver* shows two changes: fatty degeneration and siderosis. The fatty change may be extreme. The yellow granules of hemosiderin, which give the Prussian blue reaction for iron, are mainly deposited in the liver cells, especially in the outer two-thirds of the lobule. They are present, but to a lesser degree, in the Kupffer cells. Myeloid areas may be present; these are discussed below. The *spleen* is usually slightly enlarged; during a relapse it may be red and markedly swollen. The chief microscopic change is evidence of marked phagocytic activity on the part of the reticulo-endothelial cells, which contain pigment and fragments of red blood cells. These changes are most pronounced during a relapse. There are also deposits of iron pigment, but the siderosis is not nearly so marked as in the liver. It is evident that though the spleen may play a part in destroying the red cells, it is the liver which stores the blood pigment. Small islands of myelocytes and nucleated red cells are occasionally present. The *lymph nodes* show no special change. In the *kidneys*, as in the liver, there is a combination of fatty degeneration and hemosiderosis. This combination may be seen in lesser degree in many of the other organs.

The *bone-marrow* changes are by far the most important. There is a very marked erythroblastic reaction, as a result of which the yellow marrow becomes red and resembles red currant jelly. This change is patchy, so that examination of a small piece of marrow may be quite misleading. The marrow of one long bone may be red, while in another it is quite yellow, or the change may only affect part of the marrow of a bone. The hyperplasia always involves the femur before the tibia. During a remission the marrow of the tibia may be normal, while that of the femur shows marked hyperplasia. The earliest change is seen in the upper end of the femur and humerus, regions in which normally there is a certain amount of red marrow. As a result of the hyperplasia the trabeculae of the medullary cavity are absorbed and the cavity may be enlarged at the expense of the shaft.

The microscopic picture is quite different from that of the functional hyperplasia which follows hemorrhage. The latter is a normoblastic reaction, whereas the reaction in pernicious anemia is of the megaloblastic type. (Fig. 411.) The megaloblast changes directly into a macrocyte, with loss of the normal multiplication which should occur at the normoblastic level. Megaloblasts have no place in the development of normal red blood cells in extra-uterine life, but only when the normal activity of the hemopoietic principle of the liver is lacking. This explains the drop in the red cell count and the relatively few normoblasts in the circulatory blood. This reaction is the one and only pathognomonic finding in the disease. During a remission there is a return to the normoblastic type of reaction. It must not be thought that the megaloblasts are the only cells of the hyperplastic marrow. Primitive white cells (myelocytes and myeloblasts) are always numerous, and at first sight it is remarkable that such numbers of



primitive leucocytes in the marrow can be associated with a marked leucopenia. The answer to the riddle is that the white cells, like the red cells, fail to mature, and until they mature they are unable to enter the circulation. It looks as if some factor (possibly a liver factor) which is normally responsible for the maturation of myelocytes into polymorphonuclears is lacking in pernicious anemia. Adult polymorphonuclears are much less numerous in the marrow of pernicious anemia than in the normal marrow. The megakaryocytes are reduced in number, and those which are present are small and degenerated; this explains the thrombocytopenia. Phagocytic cells containing hemosiderin or erythrocytes are prominent during a relapse.

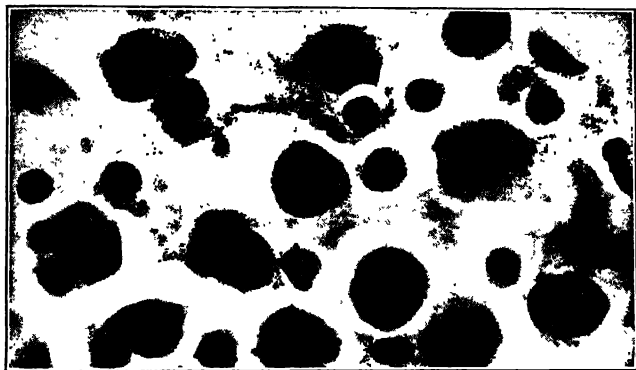


FIG. 411.—Megaloblastic reaction of the bone-marrow in pernicious anemia. All of the cells are either megaloblasts or normoblasts.  $\times 1000$ .

*Extramedullary blood formation* may occur, but it is difficult to know to what extent. Before the fifth month of fetal life the blood is formed by the liver and spleen. When there is great demand for more blood in pernicious anemia small islands of myeloid tissue may develop in the liver and possibly in the spleen. It is doubtful if these extra-medullary foci play a part of any importance, for even in severe exacerbations it will seldom be found that all the bone-marrow of the body is hyperplastic.

The lesions of the *alimentary tract* affect chiefly the tongue and stomach. Soreness of the tongue is a frequent feature of the early stage of the disease. At the time of death there may be a severe glossitis, the tongue being fiery red and resembling a beefsteak. In more chronic cases the tongue is atrophic and smooth as if it had been ironed, with disappearance of the papillæ and atrophy of mucous membrane and muscle. It has been suggested that the tongue lesions are a manifestation of avitaminosis, because rather similar lesions can be produced in animals by means of deficient diets. The upper two-thirds of the stomach show severe atrophy; in some cases the wall may be no thicker than parchment, so that the diagnosis may be made with the naked eye. The atrophy involves all of the coats (Fig. 412),

and in the mucosa the specialized oxyntic and peptic cells have disappeared. At the junction of fundus with pyloric mucosa there is an abrupt change to normal thickness. The mucosal changes probably have an etiological relationship to the anemia. Atrophic and ulcerative lesions used to be described in the intestine, but it is now known that these are postmortem in origin, and are not seen if formalin is injected into the abdomen immediately after death.

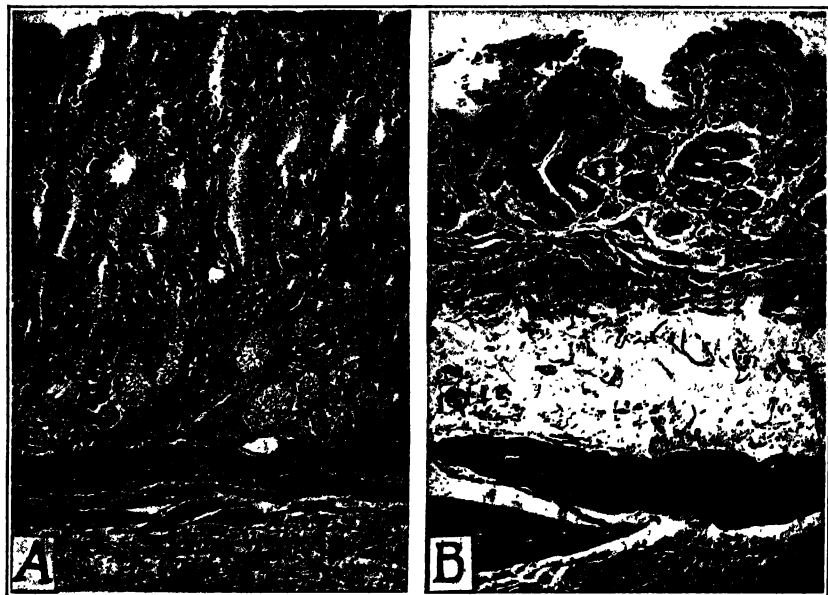


FIG. 412.—Comparison of normal stomach wall (A) with that of pernicious anemia (B).  
 X 65.

*Spinal cord lesions* occur in about 5 per cent of the cases. It is a subacute combined degeneration, affecting both posterior and lateral columns, more especially the former. The cord is swollen, and shows translucent patches first in the posterior columns, then the lateral columns, and finally the anterior columns. *Microscopically* there is breaking up and degeneration of the medullary sheaths, followed later by disappearance of the axis cylinders. The lesions are shown by means of the Weigert myelin sheath stain. These changes are responsible for the ataxia and spasticity already described. The cord lesions bear no relation to the severity of the anemia, and may appear before any anemia can be detected. Nor are they responsible for the numbness, tingling, and paresthesias which are so common an accompaniment of the anemia.

**Nature of the Disease.**—In pernicious anemia the normal factor which stimulates maturation of the red cells of the marrow (hemopoietic principle) is absent. The marrow is packed with immature cells which

are unable to enter the blood stream in any numbers. To borrow a catchword from the political economist, there is poverty in the midst of plenty. The hemopoietic principle, though stored in the liver and also in the stomach and kidney, is produced in the stomach during the process of digestion. As the result of the brilliant investigations of Castle it would appear that the hemopoietic principle is produced by the interaction of two factors, an intrinsic factor in the gastric juice and an extrinsic factor in the protein of the food (meat). The intrinsic or gastric factor is not the acid nor the pepsin of the gastric juice, but some specific factor so far unrecognized. The absence of this factor is associated with achlorhydria, although there may be no free acid in the gastric juice for many years before the development of anemia. Other members of the family may show achylia without anemia, indicating the hereditary character of the defect. The hydrochloric acid is first lost, then the pepsin, then the mucus and finally the intrinsic factor. The basis of these changes may be the atrophy of the gastric mucosa. Some evidence suggests that the extrinsic factor in the food may be vitamin B<sub>2</sub> (Strauss and Castle) but this matter is by no means settled. It is evident that even though intrinsic and extrinsic factors are present there may be symptoms of deficiency on account of lack of absorption of the hemopoietic principle from the intestinal tract. The macrocytic anemia of some cases of sprue and coeliac disease may be explained on this basis, although in others there is evidence of deficiency in the extrinsic factor.

It has been suggested that the argentaffin cells of the stomach are concerned with normal erythropoiesis. These cells are present in the pyloric and cardiac portions but not in the fundus. They are completely or almost completely absent in cases of pernicious anemia (Jacobson).

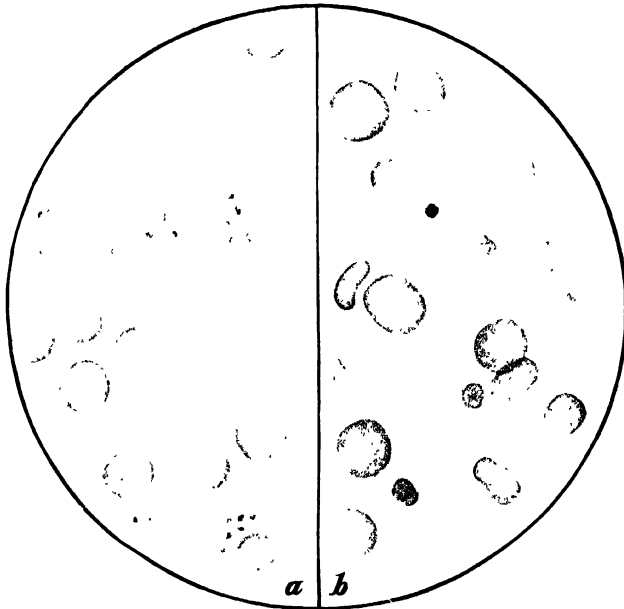
But what of the spinal cord lesions? They can certainly not be attributed to the effect of the anemia, for they may develop before the anemia. Some writers believe that the blood and marrow changes are caused by a deficiency, but that the spinal cord changes are the result of toxic action. Mellanby suggests, and this appears more probable, that there are two deficiency factors, one for bone-marrow, the other for the spinal cord. It is possible that the cord factor may be vitamin B<sub>1</sub>. Clinically either deficiency may appear before the other, and there is no relationship between their severity.

*Other macrocytic anemias* must be mentioned before closing this discussion. Of these the most important are the anemia of sprue, of Dicrocoelium, and of pregnancy. *Sprue* is a tropical intestinal infection characterized by abdominal distention, the passage of large pale bulky stools with a high fat content, atrophy of the tongue and the intestinal mucous membrane, gastric anacidity in about one-half the cases, and the development of a blood picture which may be indistinguishable from that of pernicious anemia. The anemia is macrocytic and the reaction of the marrow is megaloblastic in type. It seems probable that the intestinal lesions (thinning and atrophy of

the mucosa, disappearance of the epithelium) may so interfere with absorption that a condition of chronic deficiency develops, with the same effect on the marrow as in pernicious anemia. Other tropical macrocytic anemias are due to lack of the extrinsic factor in the food of poorly nourished natives. *Deficiency in folic acid*, a new synthetic member of the vitamin B complex, leads to macrocytic anemia and severe granulocytopenia in the experimental animal. This can be induced by means of succinyl-sulphathiazole, which inhibits the bacterial synthesis of folic acid in the intestine. There is progressive hypoplasia of the marrow involving both the erythroid and myeloid series (Endicott *et al.*). The administration of folic acid has proved of striking value in the treatment of macrocytic anemia. *Dibothriocephalus latus* is a common parasite among fish-eating peoples. A very small percentage of such infected persons develop a macrocytic anemia identical with pernicious anemia. Achlorhydria is present in over 80 per cent of these patients. If the worm is expelled, the patient is cured, but the blood can be brought back to normal by means of liver treatment, even though the worm is still present in the bowel. Some additional factor besides the worm must be necessary to produce the anemia, possibly absence of something akin to the pernicious anemia-preventing principle. Fish tapeworm infestation is very common in Japan but is never associated with anemia, and pernicious anemia is also unknown in that country. Most of the cases of *Dibothriocephalus* anemia occur in Finland, suggesting that there may be some racial factor. In *pregnancy* a small number of women develop an anemia identical with pernicious anemia during the later months of pregnancy and in the early puerperium (this must not be confused with the common hypochromic anemia of pregnancy). It responds in the usual way to liver treatment, and the prognosis is much better than in pernicious anemia. *Gastrectomy* may be followed by macrocytic anemia if the acid-bearing part of the stomach has been removed. Diffuse disease of the liver such as *cirrhosis* may interfere so much with storage of the hemopoietic principle that the same type of anemia may sometimes develop.

**Iron-deficiency Anemias.**—Any anemia which responds to adequate doses of iron may be classed as an iron-deficiency anemia. The total amount of hemoglobin is low, but the red blood cells are not diminished in equal proportion, so that the color-index is low and the anemia is *hypochromic*. The red cells may be smaller than normal (*microcytic anemia*) or of normal size. There are two supplies of iron for the manufacture of hemoglobin: (1) the food, and (2) the iron stores in the liver, spleen and bone-marrow. In health only minute quantities of iron are absorbed, but in experimental iron-deficiency large amounts are absorbed. The course of the iron can be followed by rendering it radio-active and thus labelling it (Hahn). Absorption occurs mainly from the duodenum, and as this is dependent on gastric acidity it is evident that achlorhydria will often be associated with hypochromic anemia.

PLATE XXIV



*a.* Hypochromic Anemia

The cells are pale and none are larger than normal. Platelets are present.

*b.* Hyperchromic Anemia

Film of pernicious anemia showing macrocytosis as well as poikilocytosis, anisocytosis and hyperchromia. There are no platelets.



Iron-deficiency anemia may be caused: (1) by blood loss, (2) by deficient iron intake, and (3) by a demand so great that absorption and the iron stores are unable to satisfy it. *Blood-loss* factor needs continual emphasis. A man may slowly lose half his blood and make it up again, but in doing so he has exhausted his store of iron, and any further loss of blood will produce anemia. Gastric and uterine hemorrhage are common causes of continued blood loss. *Deficient intake* may be due to poverty, faulty dietary habits, or organic disease of the stomach and esophagus. *Excessive demand* is physiological and depends on age and sex. There is an increased demand for iron during the first two years of life, and on account of menstruation, pregnancy and lactation. For these reasons hypochromic anemia is common in infancy and in women during the reproductive period. Bottle-fed babies get an infinitesimal amount of iron, and prematurity may have prevented the accumulation of a sufficient store of iron.

**Primary Hypochromic Anemia.**—Many names have been given to this condition, *e. g.*, idiopathic hypochromia, simple achlorhydric anemia, chronic chlorosis, etc. The condition is a disease of middle-aged women, among whom it is a more common cause of ill-health than pernicious anemia. It often follows pregnancy, or rather the anemia is a continuation of the anemia which normally occurs in the later months of pregnancy. Occasionally it may occur in men. It is remarkable for its chronicity, an average period being ten years. The patient presents a curious combination of the clinical picture of pernicious anemia and the blood picture of hypochromic anemia. Digestive symptoms are marked. There is evidence of gastritis—poor appetite, frequent absence of free hydrochloric acid in the stomach, and much mucus in the stomach contents so that the gastric juice is very viscid. The tongue is bald and glazed even more commonly than in pernicious anemia; in the severe cases it is angry and red. The nails often present a very characteristic appearance; they are dry and brittle, longitudinally striated, and turned up at the edges so that they become “spoon-shaped,” a change never seen in pernicious anemia. Paresthesias such as numbness and tingling may be present in the arms and legs. The spleen is often palpable, but is never greatly enlarged. The triad characteristic of the disease is anemia, atrophy of the mucous membrane of the tongue, and brittleness or spoon-shaped deformity of the nails.

The *blood changes* are the reverse of those of pernicious anemia, although the symptomatology is so similar. In pernicious anemia the anemia is hyperchromic in type, but in this condition it is achromic. In the former disease the bone-marrow reaction is megaloblastic, and in the latter it is normoblastic. The red cells are diminished in number, but the decrease in hemoglobin is still greater, so that the color index is low and hypochromia (achromia) is marked. (Plate XXIV, A and Fig. 414.) The average diameter of the red cells is smaller than normal, while in pernicious anemia it is greater than normal. (Fig. 413.) It is therefore a *microcytic anemia*. There is no evidence of hemolysis

(tingeing of the blood serum, increase of the icterus index), as compared with the hemolysis characteristic of pernicious anemia. There is leucopenia, relative lymphocytosis, and thrombocytopenia.

The *cause* of the condition is an iron deficiency, as a result of which (1) the stimulus necessary for the normal maturation of the normoblasts is lacking, so that they are unable to develop into erythrocytes quickly enough, and (2) the hemoglobin molecule is not properly built up in the normoblasts. The result is a stuffing of the marrow with normoblasts, and a deficiency of red cells in the blood, those present being poorly supplied with hemoglobin. The basis of the deficiency appears to be failure in the absorption of iron, which in turn is due, at least in part, to the hypochlorhydria, as the presence of acid is necessary for the solution and absorption of iron. The administration



FIG. 413

FIG. 413.—Hyperchromic anemia (pernicious anemia). The cells are macrocytic.  $\times 1000$ .

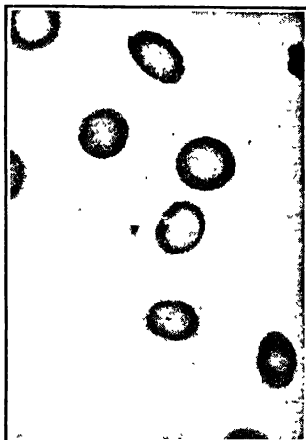


FIG. 414

FIG. 414.—Hypochromic anemia. The cells are microcytic.  $\times 1000$ .

of large amounts of iron, especially when combined with small amounts of copper, has the same dramatic effect as liver treatment in pernicious anemia. The reason for the massive doses of iron far in excess of the needs of the body (the total amount in the body is about 3 grams or the amount in a large nail) appears to be that solubility, greatly diminished by the absence of acid, is accelerated by the presence of excess of iron. One form of hypochromic anemia among the poorer classes is due to a lack of iron in the diet, particularly in women in relation to pregnancy and menstruation. Anemia in young children may be of this type, as milk is poor in iron. Sex is an important factor, because of the loss of menstrual blood and the fact that during pregnancy much of the maternal iron is stored in the fetus.

The so-called *Plummer-Vinson syndrome* is practically the same disease with the addition of dysphagia. It occurs in middle-aged



women, although occasionally in men, and is characterized by hypochromic anemia, dysphagia, dryness and atrophy of the mucous membrane of the tongue, pharynx, and esophagus, painful cracks at the angles of the mouth, achlorhydria, brittleness of the nails, and enlargement of the spleen. There is a tendency for the condition to act as a predisposing cause of cancer of the hypopharynx in women. Owing to the dysphagia the patient will be found to have been living on slops for a prolonged period, and the anemia is doubtless due to the deficiency of iron in the diet. It responds remarkably to the administration of iron.

**Chlorosis.**—Chlorosis, or “the green sickness” (*kloros*, green), used to be one of the commonest of diseases; now it has become remarkably rare, and is one of the best examples of a disappearing disease. Only women are affected, so that chlorosis presents one of the best examples of a disease with a very marked sex incidence. It usually develops shortly after puberty, but may appear at any time between the age of fifteen and twenty-five years. It was formerly known as “the disease of virgins.” It is a deficiency anemia due to lack of iron. Three causal factors may be considered: (1) an insufficient intake of iron in the food, (2) loss of iron by menstrual and other blood loss, (3) undue demand for iron by the growing organism. The disease is really an exaggeration of a physiological change which occurs in over 10 per cent of girls at the time of puberty. Its disappearance seems to be due to the emancipation of women from a sedentary cloistered existence. Severe cases are now rare, but mild degrees are not uncommon, although they are now correctly called hypochromic anemia. Iron cures the disease.

**Pyridoxine Deficiency Anemia.**—An interesting link between the two principal forms of nutritional anemia in man, namely, pernicious anemia and iron-deficiency anemia, is provided by experimental pyridoxine deficiency anemia in swine (Wintrobe, *et al.*). When the diet of the pig is lacking in pyridoxine but adequate in all the other elements of the vitamin B complex, the animal develops a severe anemia characterized by microcytosis, polychromatophilia, reticulocytes and nucleated red cells in the blood, a rise in the serum iron, hemosiderosis and bone-marrow hyperplasia. The microcytic anemia resembles that due to iron deficiency, whilst the hemosiderosis and elevated serum iron suggest pernicious anemia. It is evident that in the pig pyridoxine plays some essential part in erythropoiesis and the synthesis of hemoglobin.

**Anemia of Infection.**—Anemia is a feature of many chronic infections, a striking example being subacute bacterial endocarditis. It seems probable that the anemia is due to some abnormality of hemoglobin synthesis apparently dependent on the presence of infection rather than to hemolysis or aplasia of the marrow. Such anemias are refractory to iron and liver therapy. Wintrobe and his associates have shown that in this condition the plasma iron is very much below normal, nor does the administration of iron raise the plasma iron as it does in the normal person. There appears to be a failure in the utilization of iron for hemoglobin regeneration during chronic infections due probably to some unknown “persistent and urgent demand for iron to fulfill some function in relation to infection which has a greater priority for iron than hemoglobin formation.” There is reason to believe that iron accumulates in inflammatory tissue and in the reticulo-endothelial system in experimental infections.

In reviewing the various forms of nutritional anemia it seems justifiable to say that they are all due to some form of deficiency. (1) The deficiency may be in the food. (2) The food may be adequate,

but the stomach may be unable to utilize what is presented to it, the most obvious example being cases of gastrectomy. (3) And finally the defect may be in the liver. In pernicious anemia there is an abundance, indeed a surplus, of hemoglobin pigment and iron; the real lack seems to be in the constituents of the stroma of the red cells. The cells are therefore hyperchromic. In the hypochromic anemias, on the other hand, there is a deficiency of iron and the hemoglobin molecule is not properly formed.

### APLASTIC ANEMIAS

Aplastic anemia may be primary or secondary. The *primary form* is fortunately a rare disease occurring in young people usually between the ages of fifteen and thirty years. It is very acute and extremely fatal, killing the patient in a few weeks, or at the most some months. Fever is very common, due probably to interference with the heat-regulating mechanism. The cause is unknown. Some agent depresses the activity of the bone-marrow until no more blood is formed. The normal amount of blood destruction is going on, but there is nothing to take the place of the destroyed erythrocytes. The anemia becomes extreme, but the blood film remains strangely normal; there are none of the changes such as the presence of macrocytes, nucleated red cells, polychromatophilia, reticulocytes, etc., which indicate that the marrow is struggling to make good the wastage. All the formed elements of the blood are diminished, the leucocytes and platelets as well as the red cells. On account of the extreme thrombocytopenia purpuric hemorrhages form an important feature of the clinical picture, and it may be very difficult to distinguish the condition from true purpura hæmorrhagica. The color index is below normal, but not extremely low. There is no evidence of hemolysis such as an increase of bilirubin in the blood or the appearance of urobilinogen in the urine. The red bone-marrow is profoundly aplastic, consisting of little more than fat, and contains very few cells (Fig. 415), but some islands of hyperplasia may be found. Some workers (Rhoads and Miller, Thompson) described a hyperplastic marrow as a frequent finding in aplastic anemia. This introduces an element of confusion into an otherwise clean-cut entity, and it seems more correct to regard such cases as examples of aleukemic leukemia. The pathological criterion of aplastic anemia is aplasia of the bone-marrow.

The *secondary form* of aplastic anemia is usually due to exhaustion of the marrow. In the end-stage of pernicious anemia the marrow may give up the fight, so that no hyperplasia may be found at autopsy and regeneration forms of red cells are absent from the blood. Severe and continued toxic conditions, poisons such as benzol and trinitrotoluol, and roentgen-rays may all injure the marrow so severely as to lead to an aplastic form of anemia. *Myelophthisic anemia* is a variety of secondary aplastic anemia in which the erythrogenic tissue of the marrow is replaced by tumor growth. This may be primary (multiple myeloma, Ewing's tumor) or secondary (carcinoma of the breast,

prostate, kidney, lung, thyroid). In the rare condition known as osteosclerosis in which the bone is thickened and the marrow reduced, an aplastic anemia (osteosclerotic anemia) may develop. In carcinomatosis of the bone-marrow there may be a picture of *leuco-erythroblastic* anemia, *i. e.*, nucleated red cells and myelocytes appear in the blood even when the anemia is slight; the anemia may be hemolytic in type (Waugh). These features may be of diagnostic importance.

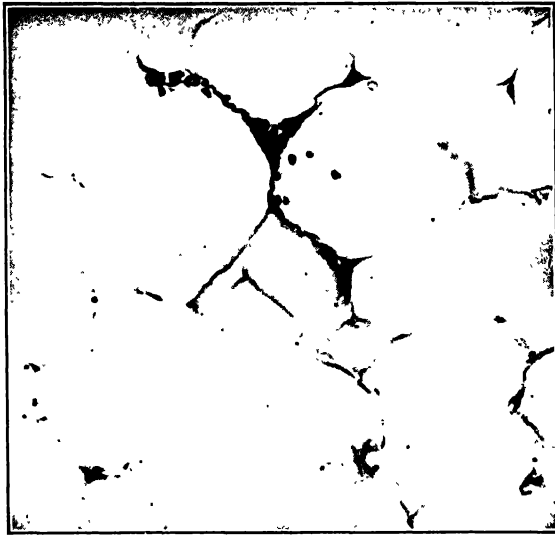


FIG. 415.—Bone-marrow in aplastic anemia, showing complete absence of hyperplasia.  
× 275.

**Secondary Anemia.**—Not so long ago one of the main groups of the anemias was that known as secondary. This term may well be given up. It signified the anemias due to loss of blood and those associated with interference with blood formation owing to direct injury to the red marrow or to constitutional diseases such as nephritis, subacute and chronic infections, and cancer. The former is a hypochromic microcytic anemia and the latter a normochromic normocytic anemia. Neither is benefited in the slightest by liver or iron therapy.

### THE HEMOLYTIC ANEMIAS

The hemolytic anemias may be divided into primary, or idiopathic, and secondary groups. In the secondary group hemolysis occurs as the result of snakebite, malaria, and infection with hemolytic streptococci, and it forms a characteristic feature of pernicious anemia. The chief members of the primary group are hemolytic jaundice, sickle-cell anemia, and erythroblastic anemia. To these may be added paroxysmal hemoglobinuria.

**Hemolytic Jaundice.**—This is also known as acholuric jaundice, because no bile appears in the urine. Although jaundice is the most striking clinical feature, the condition is really a hemolytic anemia,

and so is considered in this place. Two forms may be recognized, a more common congenital type (Minkowski-Chauffard type) and a rare acquired type (Hayem-Widal type). The acquired type comes on later; it is more severe, the anemia is more marked though the jaundice is much less, splenectomy does little good, and the increased fragility of the red cells, so characteristic of this form of anemia, is very slight; the blood contains hemolysins in the acquired but not in the congenital form. In the so-called *Lederer type* of acute hemolytic anemia fragility is generally normal. Its outstanding characteristic is that whilst there is a high mortality in untreated cases, transfusion cures the disease. The description which follows applies to the congenital form.

The disease is both familial and congenital, though it may not appear until the second decade. One case is reported in which the disease remained latent until the age of seventy-five years, when treatment by splenectomy was successful (Mandelbaum). Some members of the family may have fragile red cells, but no anemia or jaundice. The jaundice persists throughout life, usually in mild form but with occasional exacerbations due to the characteristic "crises," in which there is increased blood destruction with attacks of pain in the region of the liver and spleen. The jaundice is due to increased production of bilirubin owing to excessive blood destruction. There is therefore an excess of bilirubin in the stools, increased production of urobilinogen, which is excreted in the urine, but bilirubin does not appear in the urine, hence the name acholuric jaundice. The blood gives an indirect van den Bergh reaction. Gall stones of the pure bilirubin type without any admixture of cholesterol are frequently present. The spleen is considerably enlarged. The long bones show longitudinal striation and a patchy moth-eaten appearance in the roentgen-ray picture, owing to osteoporosis produced by the hyperplastic marrow.

The *blood* shows a secondary anemia, usually mild, but severe in the crises. The patient may have a count as low as 3,000,000, and yet be without symptoms and able to play his part in the world. If the anemia becomes severe it may closely resemble the pernicious anemia type. The two chief characteristics of the film are microspherulocytes and reticulocytes. A spherulocyte is smaller and thicker than normal; it is spherical instead of biconcave. This characteristic can be recognized in wet preparations; in dry smears the cells merely appear as densely stained microcytes. Haden has shown that this increase in thickness is related to the increased fragility (see below), and that microspherulosis is the fundamental inborn error in congenital hemolytic jaundice. As biconcave cells become globular when placed in hypotonic saline, it is evident that the more globular cells will rupture more readily. "The anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte." (Haden.) Reticulated red cells are more numerous than in any other disease. In place of the usual 1 per cent there may be 20 per cent; in the acquired form there may be 50 per cent or more. This is an indication of compensatory bone-marrow activity. The

white cells share in this activity, and the leucocyte count is generally from 12,000 to 15,000. In crises it may go up to 80,000. Normoblasts may be numerous, and these may be mistaken for leucocytes in the counting chamber and cause error in the count. There is an increased fragility of the red cells, *i. e.*, they are hemolyzed by salt solution of a strength which leaves normal red cells untouched. According to Lord Dawson, the fragility is normal in 10 per cent of cases, but my own impression is that this number should be higher. It is only the small spherical cells which are abnormally fragile, and these are selectively removed by the spleen where they are found in large numbers. If Knisely's work (see page 793) is correct, it is possible that the basis of hemolytic jaundice is increased activity in the separation and storage of erythrocytes, with resulting spherulocytosis.

**Lesions.**—The most striking change is in the spleen, which is markedly enlarged and weighs about 1000 grams. It is firm and of a bright red color like a beefsteak. It is stuffed with blood, so that after removal it loses considerably in bulk unless the vessels are clamped. The capsule is thickened. *Microscopically* the pulp is entirely occupied by red cells, thus presenting a very characteristic appearance. The sinuses are empty, and the lining cells may resemble glandular epithelium. This arrangement of crowded pulp and empty sinuses is the reverse of what might be expected from Knisely's observations, but it may be accounted for by the rapid agonal outpouring of red cells from sinuses into pulp which is known to occur. On the other hand it may be more realistic to accept this fact as disproof of the idea that increased separation of erythrocytes from plasma is the basis of the increased fragility. Another similar fact which might be cited is the lack of effect of splenectomy on the fragility and spherulocytosis, although it may cure the jaundice. The phagocytic cells contain a large amount of hemosiderin, especially during the hemolytic crises. The other reticulo-endothelial organs (liver and bone-marrow) also show hemosiderosis, as do the epithelial cells of the liver and kidney. The yellow bone-marrow is hyperplastic and bright red; the hyperplasia is normoblastic in type and compensatory in character. I have even seen extramedullary erythropoiesis in the spleen.

**The Relation of Symptoms to Lesions.**—The essential symptoms are anemia and jaundice; the essential lesions are splenomegaly and hemosiderosis. The connecting link between the two groups is the increased fragility of the red cells, which itself is due to spherulocytosis. Owing to this fragility the red cells are unduly exposed to the inimical influence of the reticulo-endothelial cells, particularly those of the spleen, and are thereby broken down. Removal of the spleen removes one of the chief destructive agents and thus produces a clinical cure. "The hemolytic diseases are the children and the spleen is their mother, but the father is still unknown and possibly there are several fathers." The presence of bilirubin calculi is to be explained by the excess of bilirubin in the blood and in the bile. The acholuria is due to the fact that the hemolytic type of bilirubin is unable to pass through the renal filter.

**Sickle-cell Anemia.**—This condition bears such a strong resemblance to hemolytic jaundice that the two should be considered together. Both are familial and hereditary. Both are characterized by a hemolytic type of

anemia, acholuric jaundice, hemosiderosis, and the appearance of large numbers of reticulocytes. In both there is some defect in the composition of the red cells. Splenectomy may cure the clinical symptoms of both, but in neither is the underlying weakness improved, in the one case the spherical character of the red cells, in the other the sickle-shaped deformity of these cells. The disease is apparently confined to the negro, but the white man may show a tendency to sickle-cell formation. In the negro the disease may show an

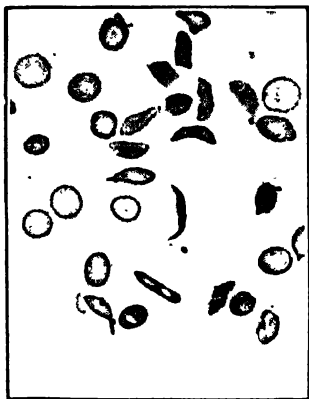


FIG. 416.—Sickle-cell anemia. Many erythrocytes are sickle-shaped.  $\times 500$ .

active or a latent phase, the latter representing the sickle-cell tendency. The *active phase* is marked by a fairly severe anemia, leucocytosis, hemolytic jaundice, increase of bilirubin in the blood and of urobilinogen in the urine. The film may show large numbers of crescentic or sickle-shaped red cells (Fig 416), and many reticulocytes. Sick cells can be shown in the *latent phase* by keeping a moist film sealed for a number of hours; as the oxygen tension diminishes the red cells become distorted and sickle-shaped. Moreover it is the exception, not the rule, for active cases to show numerous sickle cells, although tailed and pointed forms are present. Countless cases have been missed in the past through lack of use of the moist film. In addition to the blood changes the active stage may be marked by fever, joint and muscle pains, and enlargement of the spleen and liver. Chronic ulcers are very common in the lower half of the leg.

The *lesions* are indefinite. There may be pools of blood around the Malpighian bodies of the spleen, due in Rich's opinion to a congenital malformation of the sinuses. There is a general siderosis as well as siderotic nodules in the spleen. The red cells in the vessels are distorted. Osteoporosis may be present.

**Erythroblastic Anemia.**—This disease goes by a variety of names, such as anemia pseudoleukemica infantum, von Jaksch's anemia, but is now commonly known as Cooley's anemia. It is characterized by a constant familial and racial incidence, a typical facial appearance, distinctive changes in the bones, and enlargement of the spleen. It usually appears in the first two years of life and sometimes in the new-born. The familial (hereditary) incidence is marked; it has been reported in identical twins. It is a disease of the Mediterranean races, most often in Greeks, but also in Italians, Armenians, and Sicilians. The skin is yellow, the face mongoloid, the head enlarged, the abdomen prominent, the stature stunted. Owing to hyperplasia of the marrow the bones show medullary trabeculations in the roentgen-ray picture, and the skull is thickened by the thick diploë. There is a moderate or marked anemia, the platelets are increased, and there is a leucocytosis which may reach 50,000. The pathognomonic feature is the presence of great numbers of nucleated red cells, both normoblasts and megaloblasts. In one case in the new-born there were 90 per cent of erythroblasts. The immature red cells suffer at the hands of the reticulo-endothelial cells, which accounts for the anemia and the deposits of hemosiderin in the spleen, liver, pancreas, and other viscera, almost like hemochromatosis. Excessive erythropoiesis is present in the marrow and in the spleen and liver. The course is usually chronic and may last a number of years.

**Paroxysmal Hemoglobinuria.**—This rare condition is characterized by sudden attacks of fever and chills accompanied by the appearance of hemoglobin in the urine. There are two etiological factors, *syphilis* and *exposure to cold*. The exposure to cold may be very slight, such as washing the hands in cold water or even drinking cold water. Usually cold weather is needed, and the

most bloody urine that I have seen was passed on a day of 60 degrees of frost. Shortly after exposure to cold the patient develops pain in the muscles and abdomen, followed by severe chills and fever. The urine is full of hemoglobin and may be of a port-wine color. It contains no well formed red cells, but numerous ghosts of hemolyzed cells; the urine is therefore clear, not smoky or cloudy as when it contains ordinary blood. The spectroscope shows the absorption bands of oxyhemoglobin or methemoglobin. There may be transient jaundice, due to the formation of bilirubin from the liberated hemoglobin. The spleen may be temporarily enlarged. The blood shows a hemolytic anemia, followed by very rapid regeneration. There is a transient leucopenia due to the protein shock caused by the rapid liberation of hemoglobin.

The hemolysis is due to the presence of an autohemolysin which is present in the blood of some syphilitic patients. This unites with red blood cells in the presence of complement but strange to say, only at a low temperature. When the two factors of syphilitic hemolysin and a low temperature are both present, a sudden reaction takes place with marked hemolysis and the liberation of large quantities of hemoglobin in the blood. This causes transient hemolytic jaundice and is excreted in the urine giving hemoglobinuria. Hemolysis with hemoglobinemia and hemoglobinuria may be caused by malaria, by drugs of the coal-tar series, or by blood transfusion, but in these cases the mechanism is quite different and bears no relation to cold.

The *nocturnal Marchiafava-Micheli type* of paroxysmal hemoglobinuria occurs only during sleep or is more marked at that time. The morning urine is deeply colored. The red cells are abnormally susceptible to hemolysis in plasma of increased acidity such as results from reduced pulmonary ventilation during sleep. *March hemoglobinuria* occurs on physical exertion such as short brisk walks; it has been observed particularly in soldiers.

**Congenital Hemolytic Disease.**—Hemolytic disease of the newborn is due to a reaction between the Rh factor which acts as an antigen in the red blood cells of the fetus and corresponding agglutinating antibodies which reach the fetal blood from the maternal circulation. It is an interaction of fetal antigens and maternal antibodies. The disease may take various forms, which are known by such names as congenital anemia, erythroblastosis fetalis, icterus gravis, and hydrops fetalis. The condition is essentially an Rh incompatibility, a term more descriptive than the common designation erythroblastosis fetalis, for erythroblasts may be present in excess in the fetal blood and tissues as the result of other causes (Macklin).

The red blood cells of the majority of human beings contain an agglutinin known as the Rh factor. This is so called because a similar agglutinin was demonstrated in 1940 by Landsteiner and Wiener in the red cells of the rhesus monkey. It is the rhesus factor. The presence of the agglutinin in human red cells was then demonstrated by testing them against anti-rhesus serum. The presence of the Rh factor bears no relation to the blood group (using the word in the ordinary sense) to which the patient belongs. The Rh agglutinin is not a single substance, but consists of several antigens. It is possible to divide the Rh blood type into at least 10 subtypes and probably more. Reactions as the result of the various subtypes are fortunately rare. About 85 per cent of persons possess the Rh factor so that they are Rh positive, whilst 15 per cent lack the factor and are Rh negative. There is a racial distribution of the factor as indicated by the fact that

90 per cent of negroes and 99 per cent of Chinese are Rh positive. Anti-Rh agglutinins may be formed in Rh negative persons following the transfusion of Rh-positive blood. An Rh-positive father can transmit the factor to the fetus as a simple Mendelian dominant. If the mother is Rh negative, anti-Rh agglutinins may be formed in her blood as the result of immunization or sensitization by the Rh factor of the fetus (Fig. 417).

The stage is now set for disaster in two possible forms. (1) If the mother is transfused with Rh-positive blood, even though belonging to the same general blood group, there may be an intra-group transfusion accident. (2) If the maternal anti-Rh agglutinins reach the fetal blood through the placenta, they will react with the agglutininogen in

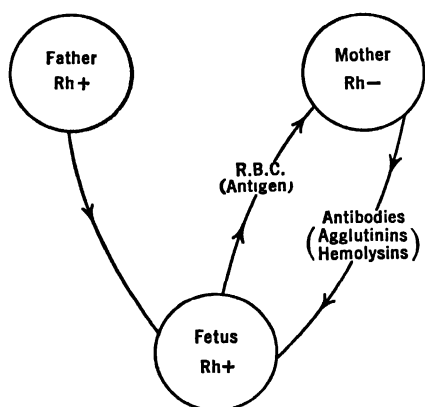


FIG. 417.—Diagram to illustrate Rh factor.  
(Courtesy of Dr. I. Erb).

the fetal red cells, as a result of which there will be a slow continuous hemolysis of those cells, although in the test tube the reaction takes the form of agglutination.

*The Rh Factor in Blood Transfusion.*—Intra-group blood transfusion reactions are usually due to the Rh factor. The danger arises if an Rh-negative person is transfused with Rh-positive blood a number of times. (In rare instances a single transfusion is sufficient.) Once sensitization occurs it appears to be permanently imprinted on the individual's

constitution, and a further transfusion years later may be followed by a severe reaction. In women an initial transfusion is not necessary, provided they have become sensitized by having had an Rh-positive child. Thus Rh-negative women who have borne children should be transfused only with Rh-negative blood.

*The Rh Factor in Pregnancy.*—In pregnancy the presence of the Rh factor in the red cells of the fetus carries a twofold threat, first to the mother and secondly to the child. The former, the danger of a transfusion reaction due to the presence of Rh antibodies in the woman's blood, has already been discussed. In the child the threat is the development of hemolytic disease of the fetus and the new-born. The chance of dangerous consequences is not as great as might be feared, as will be evident from the following figures. One out of 12 marriages involves an Rh-positive husband and an Rh-negative wife. The incidence of hemolytic disease of the infant is about 1 in 250 to 500 deliveries, that of the severe jaundiced form of erythroblastosis fetalis 1 in 1500 deliveries, and the fatal hydrops form 1 in 2000 deliveries. While the condition may arise in the first pregnancy, it



may not develop until after the tenth normal child has been born. Not all mothers who are Rh negative become sensitized by an Rh-positive fetus. The exact percentage who escape and the reason for this is unknown.

The child may be born dead, especially in the hydrops cases, it may live only a few days, or it may survive. About 7 per cent of those which survive are mental defectives. If jaundice develops it usually does not do so until some days after birth. This is apparently due to excretion of the excess of bilirubin through the placenta. In the most severe form of all, hydrops fetalis, jaundice is absent.

It sometimes happens that the titer of agglutinins in the maternal blood bears no relation to the severity of the hemolytic disease in the child. Indeed in the hydrops cases there may be an apparently complete absence of maternal agglutinins. This paradox is explained by the discovery in the maternal serum of what have been called *blocking antibodies* in addition to the usual agglutinating antibodies. The blocking antibodies interfere with the union in the test tube between the antigens and the agglutinating antibodies, so that the presence of the latter is readily overlooked.

The *clinical picture* in the child is one of *congenital anemia* with *erythroblastosis fetalis*. Jaundice may or may not be present. There are great numbers of nucleated red cells, a compensatory phenomenon, and active erythropoiesis in the liver and spleen, together with hemosiderosis in these and other organs. The child may die in the course of a few days of *malignant icterus neonatorum*. In such a case the nuclear structures of the brain show intense staining with bile ("Kernicterus"). In *congenital hydrops* the child is likely to be born dead with edema and marked ascites. The cause of the edema appears to be an increased permeability of the capillary walls due to anoxemia. The hydrops variety is associated with a greatly enlarged and edematous placenta, the surface being made up of large, friable, pale cotyledons. Microscopically the villi show evidence of immaturity, such as large size, the persistence of Langhans cells which normally disappear about the middle of pregnancy, and the presence of numerous erythroblasts in the capillaries. In the jaundiced form of erythroblastosis the changes in the placenta are similar but of much milder degree. If the fetus has died before the onset of labor and become macerated it may be very difficult to establish a diagnosis. Here again the presence of placental changes and of numerous erythroblasts in the pulmonary capillaries is of great value (Potter).

## PURPURA

Purpura is a condition in which there are hemorrhages in the skin and mucous membranes. It is a symptom or symptom-complex rather than a disease, and there are many varieties of purpura. Of these there is one which forms a definite disease entity which must be sharply

differentiated from all the other varieties, and which is usually known as *purpura hæmorrhagica*.

**Purpura Hemorrhagica.**—This is also called Werlhof's disease and primary thrombocytopenic purpura, the latter an excellent descriptive title, but a trifle cumbersome. It was described by Werlhof in 1740, but it was not until 1910 that Duke demonstrated that the essential basis of the condition was a thrombocytopenia or decrease in the number of the blood platelets (thrombocytes).

**Symptoms.**—The disease is commoner in young people of the female sex. The hemorrhages which form the chief clinical feature may be small petechiæ or large ecchymoses. There may be hemorrhages into the skin, hemorrhage from the mucous membrane of the nose, mouth, stomach, intestine, and uterus, and blood in the urine. The hemorrhage may be spontaneous or traumatic. Hemorrhage due to trauma may last for an hour or more; the bleeding-time is prolonged, but the clotting-time is normal. In hemophilia, on the other hand, the clotting-time is prolonged, but the bleeding-time is normal. A tourniquet applied to the arm so as to obstruct the venous but not the arterial flow causes petechiæ to appear below the tourniquet. The spleen may be moderately enlarged, and splenectomy may be attended by brilliant results. In this connection it must be recognized that the disease may follow an acute or a chronic course. The *acute* cases prove fatal in the course of a few weeks, and splenectomy is not of the slightest use. The *chronic* cases may go on for months or years, and for some unexplained reason there may be intermissions when the patient is free from all signs of the disease. It is in these cases that splenectomy gives the best results.

The most striking change in the blood is the thrombocytopenia. The normal number of platelets is 200,000 or 250,000 per c.mm. In *purpura hæmorrhagica* the number is usually below 60,000, and in severe cases they may entirely disappear. We can only guess at the cause of this remarkable disappearance. It seems probable that the platelets are defective in quality, just as are the red cells in hemolytic jaundice and sickle-cell anemia. They therefore fall an easy prey to the destructive and phagocytic powers of the reticulo-endothelial cells in the spleen, liver, bone-marrow, and lymph nodes. Splenectomy removes the largest collection of these cells, so that the fragile platelets are now able to hold their own. It is possible to prepare an anti-platelet serum which when injected into an animal causes an extreme fall in the number of platelets with the appearance of purpuric symptoms. It is of interest to note that in hemophilia (see p. 848) the platelets are less fragile instead of more fragile than normal. In some cases there may be no marked change in the platelet count, but in these there may be a qualitative change. In the general discussion of blood platelets we have seen that it is the small (young) platelets which are active in stopping bleeding, the larger ones being inactive. In *purpura hæmorrhagica* there may be many large and giant platelets, but although giants morphologically they are dwarfs functionally.

The blood shows other changes. There is an anemia of varying severity, depending on the degree of the hemorrhage. Leucocytosis is present after the hemorrhages. The clotting-time is normal and the bleeding-time greatly prolonged. A very characteristic feature due to the absence of platelets is loss of contraction power of the clot, so that it is unable to shrink from the side of the test-tube in which the blood is collected.

**Lesions.**—The germinal centers of the lymph follicles in the spleen are large and active. The sinuses are nearly empty, and the lining cells are swollen and may resemble glandular epithelium. A characteristic finding is the presence of megakaryocytes in the sinuses of

the spleen, and also in the liver sinusoids and other capillaries (Nickerson and Sunderland). Hyaline megakaryocytes which produce large pseudoplatelets are found only in this disease.

**The Relation of Symptoms to Lesions.**—The main symptom is the hemorrhage, the main lesion thrombocytopenia. In discussing the relation between these two it is fundamental to distinguish between spontaneous hemorrhage and the hemorrhage which follows trauma, both of which are present in purpura. The prolonged bleeding-time after an incision is due to the lack of platelets. Hemorrhage from a vessel is first arrested not by the production of fibrin but by the formation of a plug of platelets which adhere together and close the hole temporarily until a permanent clot is produced. In the absence of the platelets this all-important clot cannot be formed. The platelets also initiate the process of clotting, for when they disintegrate owing to injury they liberate the necessary thromboplastin. Only a small number of platelets are necessary for this purpose, and there are sufficient in most cases of purpura, so that the coagulation-time is normal. The excess of platelets causes retraction of the clot in some unknown way. In purpura there is no excess, so that the clot in the test tube fails to retract.

The cause of the spontaneous hemorrhage, which after all is much more common and important than hemorrhage due to trauma, remains a mystery. Presumably it bears some relation to the thrombocytopenia. It is as if the vascular pipes normally leaked, perhaps as the result of minimal trauma, but the leaks are continually plugged by the platelets. In thrombocytopenia such plugging is no longer possible. The long intermissions in the chronic cases are also difficult to explain. A final difficulty is the therapeutic effect of splenectomy. The theoretical basis for this form of treatment is the observation that removal of the spleen in a normal animal is followed by a marked rise in platelets. This occurs also in man, but in the course of a few weeks or months the platelets may fall again to their original level, and yet the patient may remain free from purpuric manifestations. There must be more in splenectomy than meets the eye. It is important to note that removal of the spleen may produce a temporary but not a permanent cure; the patient may remain well for a year or two, and then the purpuric manifestations may return. Cases should be followed for from three to five years before one can be certain that the condition is cured.

**Secondary Purpura.**—So-called purpuric hemorrhages into the skin and mucous membranes may occur in a variety of pathological conditions. Toxic injury to the vessel walls may cause such hemorrhages in septicemia and in the infectious fevers, especially meningococcus meningitis, scarlet and typhus fevers, where they form a purpuric or hemorrhagic rash. Lesions of the bone-marrow with reduction in the number of blood platelets may cause purpuric manifestations more nearly related to those of primary thrombocytopenic purpura, though the platelets seldom fall to so low a level. Widespread secondary carcinoma of the marrow, lymphatic leukemia, and pernicious anemia may produce secondary purpura of this type, but the most striking example is aplastic anemia with its great reduction in the number of megakaryocytes from which the platelets are formed.

**The Exudative Diathesis.**—In some persons there is an increased permeability of the small bloodvessels, as a result of which both plasma and red cells can pass out into the tissues. The platelets are normal. The condition is not permanent, but comes on in attacks resembling anaphylaxis. These cases are classed as *simple idiopathic purpura*,

and are subdivided into a number of clinical groups. The escape of red cells from the vessels causes purpuric lesions, but the escape of plasma may cause urticaria in the skin and even more important visceral lesions. The following forms of the exudative diathesis may be distinguished.

**Purpura Simplex.**—A mild condition of purpura occurring in children. The hemorrhages are confined to the skin and clear up in a week or two.

**Henoch's Purpura.**—In this form of the diathesis there are lesions in the skin, mucous membranes, and wall of the alimentary canal. Hemorrhage, urticaria, and erythema occur in the skin. There may be hemorrhage from the nose, stomach, bowel, and kidney. The most distinctive feature of this variety is the occurrence of transudation of serum into the wall of the stomach and intestine, thus causing pain, vomiting and diarrhea. Intussusception may occur. If the skin manifestations are absent or delayed, the patient is in danger of having his abdomen opened and his appendix removed. The occurrence of fever and leucocytosis makes this danger even greater.

**Schönlein's Purpura.**—This hardly deserves a special name. It is merely a form of the exudative diathesis in which the main manifestations are in the joints. The skin shows purpuric spots, urticaria, and erythema. There is a serous exudation into the joints causing an acute arthritis which is easily mistaken for rheumatic fever, especially as the temperature may be raised.

## HEMOPHILIA

Hemophilia, "the bleeding disease," is characterized by prolonged bleeding following a cut or trauma, but not by spontaneous hemorrhage. It is the most hereditary of all hereditary diseases, and repeats itself in generation after generation. Famous examples occurring in the royal families of Europe are known to everyone. It is almost invariably confined to males but transmitted by females of the family. It is, therefore, an example of sex-linked heredity. Birch finds that the urine of patients with hemophilia is deficient in the female sex hormone as tested by its effect in producing estrus in castrated female rats. Some workers have confirmed these results, but others have failed to do so. The hemorrhagic tendency appears in early childhood. A simple injury such as the extraction of a tooth may give rise to a fatal hemorrhage. Hemorrhage into the large joints after slight trauma is common. The hemophilic joint, usually the knee or elbow, develops a condition like chronic arthritis; some of the blood is not absorbed, and this causes proliferation of the synovial membrane and erosion of the cartilage.

The striking *blood change* is the very *prolonged coagulation-time*, sometimes several hours in length. The bleeding-time, *i. e.*, the time blood continues to flow from a minute puncture of the skin, is normal in the majority of cases, as there is no thrombocytopenia; it is the

platelets which plug such a puncture. When the clot does form, it shows normal retraction. In these respects hemophilia differs from purpura hæmorrhagica, and also in the fact that spontaneous hemorrhage is the characteristic feature of the latter but not the former. The reason why blood continues to flow from a cut but not from the puncture made in estimating the bleeding time is that hemorrhage from a cut is arrested primarily by the formation of a clot, whereas hemorrhage from a puncture is stopped by a plug of platelets. Curiously enough, the fundamental lesion in hemophilia appears to be a qualitative defect in the platelets, but it is the opposite defect to that which was found, or rather suggested, in purpura. The platelets are normal in number, but of decreased fragility. For the coagulation of blood the following elements are necessary: fibrinogen, prothrombin, calcium, and thrombokinase. The first three are present in the circulating blood, and are normal in amount in hemophilia. Thrombokinase is liberated from the platelets when the blood is shed, and also from tissue cells. The prothrombin conversion rate is extremely slow, although brought back to normal by the addition of a minute amount of organ extract containing thrombokinase. Unless the platelets break down they do not liberate thrombokinase. In hemophilia the platelets are abnormally stable and resistant. If normal blood is collected from a vein into a paraffined tube, the platelets disappear in a few minutes, as is seen in the stained smears. In hemophilic blood the platelets may be found intact several hours later. Coagulation does not occur until the platelets disintegrate. When the resistance of the platelets is overcome mechanically by means of a pestle and mortar, the blood clots normally. It would appear, therefore, that hemophilia is a hereditary defect in the platelets as a result of which they have an increased resistance, a defect which is transmitted to the male by the female of the species.

## HYPERPLASTIC DISEASES

There is a group of diseases in which there is evidence in the blood of permanent hyperplasia of the hemopoietic tissues, with overproduction of erythrocytes, granulocytes (myeloid cells), or lymphocytes. These conditions are known respectively as erythremia, myelogenous leukemia, and lymphatic leukemia. It seems probable that they are all neoplastic in nature.

**Leukemia.**—The essential feature of leukemia is a neoplastic proliferation of the leucoblastic tissues, as a result of which there is usually a great increase in the white cells of the blood. The increase may affect the myeloid cells (myelogenous leukemia), the lymphoid cells (lymphoid leukemia), or the monocytes (monocytic leukemia). Occasionally there is proliferation of white cells in the tissues, but they fail to appear in the blood stream. Such a condition is called *aleukemic leukemia*, but it would be much better to speak of aleukemic myelosis, aleukemic lymphadenosis, or aleukemic reticulo-endotheliosis, depend-

ing on which of the leucoblastic tissues is affected. It is not a separate disease entity, but merely a phase of the leukemic state, for sooner or later the blood becomes flooded with white cells: Even before this happens, abnormal types of leucocytes may be found in the blood, although the total count is not raised. The leukemia is usually of the lymphatic type. It is evident that it may be difficult or impossible to draw any sharp distinction between aleukemic lymphadenosis and lymphosarcoma, for the latter condition may also terminate with a leukemic blood picture. There can be little doubt that from the pathological standpoint these conditions are closely related.

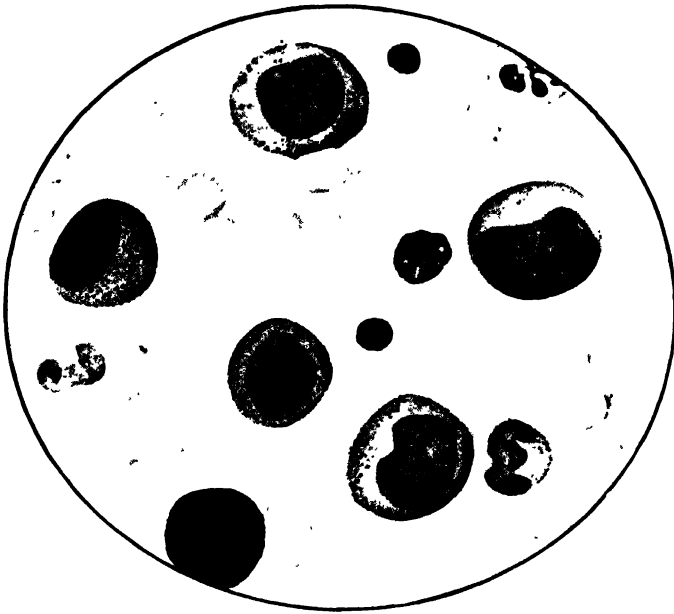
*Leukanemia* is another unsatisfactory term applied to a blood picture in which the features of leukemia and pernicious anemia are combined. The appearance is deceptive, for the case can always be shown to belong to one or the other group. In pernicious anemia primitive white cells may appear in the blood, and in leukemia megaloblasts may sometimes be found. Leukanemia is merely leukemia with severe anemia and the appearance of unusually primitive red cells in the blood.

The leukemias fall into three main groups, *myelogenous*, *lymphatic*, and *monocytic leukemias*. To these may be added a fourth, *acute leukemia*. Rare cases in which plasma cells are present in the blood and leucoblastic tissues in large numbers are known as *plasma cell leukemia*. The distinction between the fully developed and classical types is very easy. Sometimes the distinction is very difficult. The more acute the disease, the more difficult is it to be certain of the nature of the abnormal white cells, for it is the primitive blood cells which appear in the acute cases, and these lack distinguishing characteristics. It is customary to describe the different forms separately, but we shall consider them together in order to avoid needless repetition.

**The Blood.**—In all forms of leukemia there is a marked increase in the number of the white cells. But such an increase is not of itself pathognomonic. Temporary counts as high as 100,000 may be met with in infective conditions, and as the result of treatment the white cell count may fall to normal in a leukemia. Much more characteristic is the presence of immature white cells, but these also may occur in other conditions which throw a strain on the bone-marrow, and a terminal leukemoid blood picture may closely simulate an acute terminal leukemia. At the same time it must be understood that in the great majority of cases the correct diagnosis can be made without the slightest difficulty merely by a glance at the stained blood film.

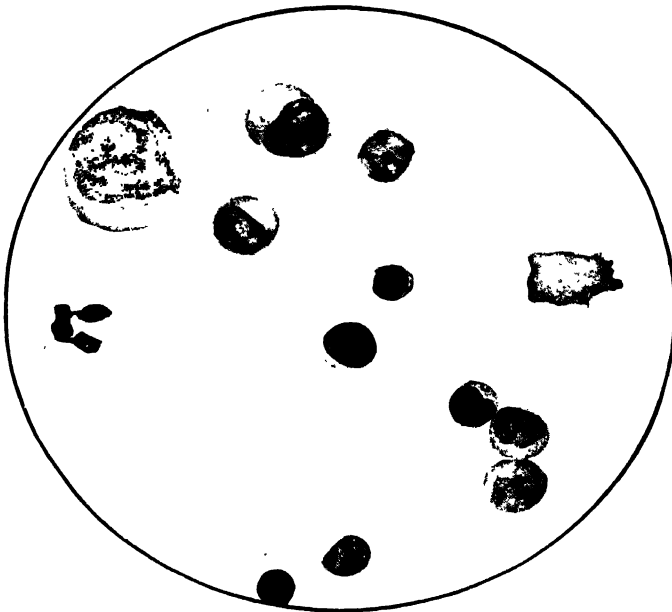
In *myelogenous leukemia* there is a great increase in the granular series of cells, both primitive (myelocytic) and adult (polymorphonuclear) in type (Fig. 418); the cells in either of these groups may be neutrophil, eosinophil, or basophil. The myelocyte usually forms the prominent feature of the film. (Plate XXV, Fig. 1). It is a large cell about double the size of the polymorphonuclear, with an indented or lobed nucleus and abundant cytoplasm containing granules which may be fine and neutrophil, or coarse and eosinophil, or basophil. More primitive leucocytes are seen in the terminal stages or in the

PLATE XXV



**Fig. 1. Myelogenous Leukemia**

Myelocytes in various stages of development, an eosinophilic myelocyte, an eosinophil, polymorphonuclears, normoblasts and platelets.



**Fig. 2. Lymphatic Leukemia**

Numerous small lymphocytes and one nuclear smudge, but no platelets.





acute form of leukemia; these are myeloblasts with non-granular cytoplasm. The total leucocyte count averages 200,000, but it may go as high as 500,000 or even 1,000,000. As a result of radiation, benzol treatment or an acute infection such as pneumonia, there may be a great drop in the cell count, sometimes to normal. All the elements of myeloid tissue tend to take part in the abnormal activity; in other words, there may be a complete myelosis. Primitive red cells, therefore, appear in the blood, and normoblasts are more numerous than in any other disease—far more numerous than in pernicious anemia. Sometimes there are macrocytes and megaloblasts in considerable numbers. In spite of this activity in the bone-marrow there is a marked and progressive anemia, owing to the erythroblastic tissue

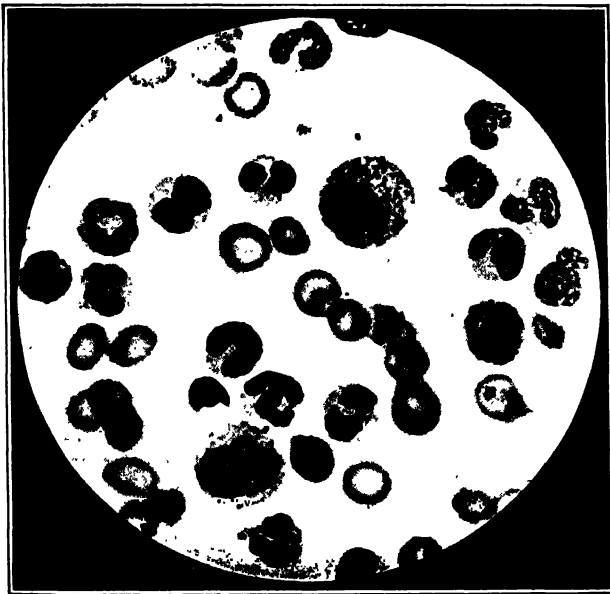


FIG. 418.—Myelogenous leukemia. Several myelocytes and very many polymorphonuclear leucocytes.  $\times 1000$ .

being crowded out by the myeloid cells. In extreme cases there may be equal numbers of red and white cells. The megakaryocytes also take part in the myelosis, and there is, therefore, a great increase of platelets in the blood, sometimes to 2,000,000. The megakaryocytes themselves may be found in the blood. If it is remembered that there may be 1,000,000 white cells, 1,000,000 red cells, and 1,000,000 platelets, some of the principal features of the blood picture may be recalled. As the lymphocytes are not formed in the marrow, the percentage count is greatly reduced.

In *lymphatic leukemia* only the lymphoid cells are increased, and may form as much as 99 per cent of the total count, although 90 per

cent is a commoner figure. (Plate XXV, Fig. 2.) The average count is 50,000 to 100,000, rather lower than in the myelogenous form. The lymphocytes contain less cytoplasm than the normal small lymphocytes, so that they may appear as naked nuclei, and the cytoplasm usually contains no azurophil granules. Many of the lymphocytes appear to be dead, so that in the slide they look like a smeared nucleus, the so-called smudge. (Fig. 419.) Primitive myeloid cells may appear in the later stages, owing to irritation of the marrow produced by deposits of lymphoid cells. Secondary anemia becomes marked when the marrow replacement reaches a severe degree, but there is none of the erythroblastic activity characteristic of myelogenous leukemia, so that there are no normoblasts or only a very few. For the same reason blood platelets are much diminished in the later stages.

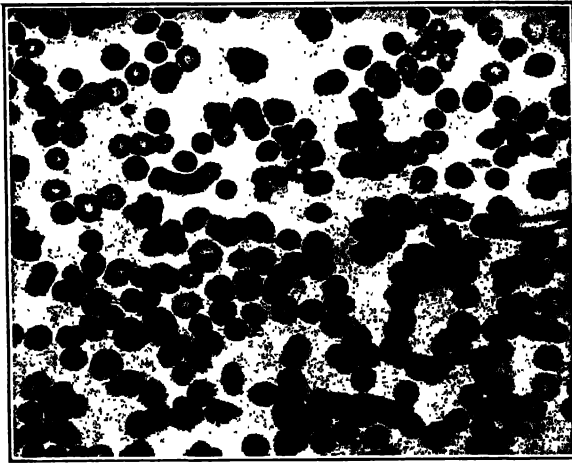


Fig. 419.—Lymphatic leukemia. Three types of cells can be seen: (1) small lymphocytes, (2) lymphocytic "smudges," (3) red blood cells.  $\times 400$ .

A consideration of the red cells and the platelets is of more use for differentiating myelogenous from lymphatic leukemia in difficult cases than is a study of the primitive white cells. Anemia is much more marked in the myelogenous than in the lymphatic form and megaloblasts are frequent. In lymphatic leukemia there is a great fall or complete disappearance of the platelets associated with bleeding, as indicated by petechiæ in the skin and occult blood in the stool and stomach contents, whereas in the myelogenous form the platelets are not greatly affected until the late stages of the disease.

A rare *monocytic leukemia* has been described, in which there is supposed to be a large increase in the number of monocytes. It is probable that at least the majority of cases represent an atypical phase of myelogenous leukemia, because a large percentage have ended as the latter disease.

In *acute leukemia* the white cell count is seldom very high, and in the early stages it may be subleukemic (below 30,000) or aleukemic. At first sight nearly all the cells appear to be large lymphocytes (Plate XXVI), and it used to be thought that most cases of acute leukemia were of the lymphatic type. It now appears probable that the acute cases are most myeloid in type and that the predominant cells are myeloid stem cells. It is often impossible to distinguish with certainty between a myeloblast and a lymphoblast, although the hematologists give a number of fine points of difference. The ordinary worker who is not a specialist in hematology will learn more by the indirect method of studying the more fully developed cells than by trying to stain stem cells by peroxidase or other special methods. If the primitive cells are myeloblasts, some myelocytes and a few polymorphonuclears will be noticed. If they are lymphoblasts the only differentiation is toward the lymphocyte. In such cases there may be very large lymphocytes with pale nuclei, the so-called Rieder's cells. When moving pictures of tissue cultures of stem cells are studied,

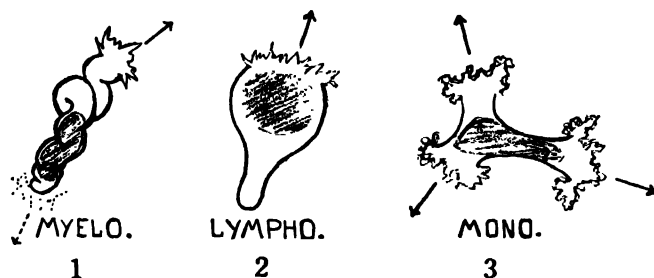


FIG. 420. Myeloblast, lymphoblast and monocyte in motion. (Rich, Wintrobe and Lewis, courtesy of Bull. Johns Hopkins Hospital.)

striking differences at once become apparent, both in form and in method of locomotion (Rich, Wintrobe and Lewis). The myeloblasts become elongated and wriggle through the culture in a highly characteristic twisting writhing worm-like manner, whereas the lymphoblasts maintain a rather fixed shape like that of a hand mirror with a tail-like process, and move forward in a steady unperturbed manner, whilst monocytes continually throw out pseudopodia bordered by a broad, filmy, undulating, ruffle-like margin, and dart now in one direction, now in another. (Fig. 420.) Roentgen-ray therapy causes an initial drop in the white cell count; when it again goes up, the cells will be much more mature and readily recognized. There is severe anemia and great diminution of the platelets. Megaloblasts may be numerous, so that in the early aleukemic stage the disease may be mistaken for pernicious anemia.

The most important feature in any form of leukemia is the presence of stem cells. These show that the case is definitely one of leukemia; the adult forms indicate the type of leukemia. Stem cells are recog-

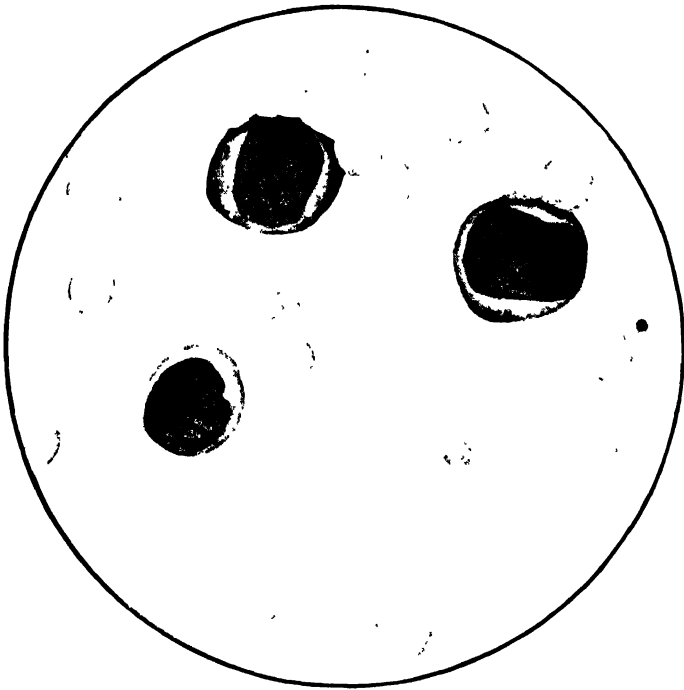
nized by their deeply basophilic cytoplasm, relatively large nucleus, and the nature of their nuclear pattern, the latter serving to distinguish them from adult lymphocytes. In the lymphocytes the nuclear chromatin forms a coarse pattern in heavy blocks, but no nucleoli can be distinguished. In contrast to this the nuclear chromatin of the stem cell is arranged in very fine strands like a sieve, and one or more nucleoli can usually be seen.

**Bone-marrow.**—In *myelogenous leukemia*, as the name implies, the basis of the disease is a leucoblastic overactivity of the myeloid tissues. The red marrow becomes filled with immature white cells, and the fatty yellow marrow is converted into actively functioning tissue. Its gross appearance varies. It is firm, and may be gray, brown, or red; sometimes it is soft and purulent. The principal cell is the neutrophil myelocyte, but the microscopic picture is a complex one, for all varieties of leucocytes and of myelocytes are present. There are also groups of non-granular myeloblasts, and these cells may enter the blood in considerable numbers in the terminal stage of the disease. The megakaryocytes are increased in number, thus accounting for the rise in the platelet count. The erythroblastic tissue is largely replaced by leucoblastic elements. In *lymphatic leukemia* the marrow is invaded by lymphoid cells. At first there are only isolated islands of lymphoid tissue, but eventually the entire marrow, both red and white, is replaced by these cells. The gross appearance is the same as in the myelogenous form. In *acute leukemia* the marrow is packed with myeloblasts, together with a few myelocytes and a very few red cells; the erythroblastic tissue of the red marrow is almost entirely replaced.

**Spleen.**—In *myelogenous leukemia* the spleen is greatly enlarged and may fill the entire abdomen, sometimes weighing as much as 10,000 grams. It is dark in color, and infarcts are common, due probably to the formation of leucocytic thrombi in the small vessels. Microscopically the lymphoid tissue has disappeared, and the pulp has the same structure as the marrow, being crowded with myeloid cells of every description. It is probable that most of these cells have been arrested by the splenic filter, but there may possibly be some myeloid metaplasia, an assumption by the spleen of its primitive blood-forming function. In the *lymphatic form* the spleen is moderately enlarged, but in the very chronic cases the enlargement may be as great as in the myelogenous form. There is extreme hyperplasia of the lymph follicles, and the pulp is replaced by lymphocytes. In monocytic leukemia the spleen, lymph nodes, and liver are slightly enlarged and are full of monocytes. In the *acute form* the spleen is enlarged to a varying degree. The more acute the process, the less is the enlargement, and in the most severe and rapid cases it may hardly be enlarged at all.

**Lymph Nodes.**—In *lymphatic leukemia* the lymph nodes all over the body are enlarged. The greatest enlargement is seen in the abdominal glands which may be as large as a walnut. The normal structure is entirely replaced by lymphocytes, and the microscopic picture cannot be distinguished from that of a lymphosarcoma. The intestinal and

PLATE XXVI



**Acute Leukemia**

Three blast cells and one nuclear smudge.



other lymphoid tissue show the same enlargement. In the *myelogenous form* the nodes are usually normal in size, although in exceptional cases they may be enlarged so as to suggest lymphatic leukemia. The sinuses are crowded with myeloid cells. In the *acute form* the lymph nodes and tonsils are enlarged and filled with myeloblasts.

**Other Organs.**—In the other organs the vessels are crowded with myelocytes or lymphocytes, depending on the form of the leukemia. Some of these cells appear to be outside the vessels, and there is often a suggestion of infiltration such as might occur in a neoplastic process. The *liver* may be moderately or markedly enlarged, and small nodules can be seen on the cut surface. These represent leukemic collections in the portal tracts, myeloid or lymphoid as the case may be. (Fig. 421.) Large numbers of the cells are outside the vessels, apparently due to an infiltrative process, but some writers consider that the appearance is due to a reversion of the liver to its primitive blood-forming

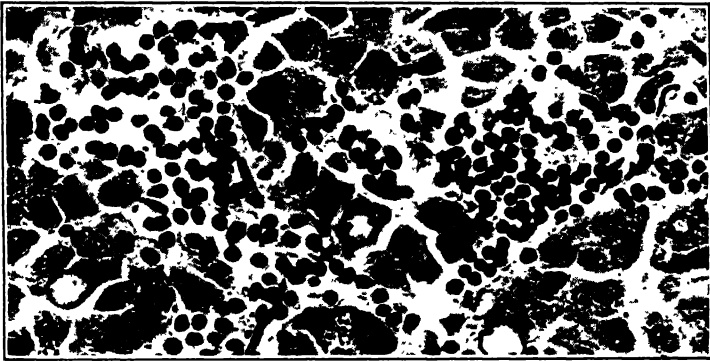


FIG. 421. —Leukemic liver. The sinusoids of the liver are widely distended with lymphocytes, the case being one of lymphatic leukemia.  $\times 400$ .

function, the immature cells being formed *in situ*. The same gross and microscopic appearance is seen in lymphatic leukemia; the cellular collections are formed of lymphocytes. The *kidneys* are pale and slightly or moderately enlarged. Here again the leukemic cells may lie outside as well as within the vessels. The heart, lungs, and other organs show a similar condition. *Hemorrhage* from the mucous membranes is a striking feature of acute leukemia, and in myelogenous leukemia there may be hemorrhage into the brain, the retina, and the middle ear.

In some cases there is marked infiltration and invasion not only of an organ but of the surrounding parts. This process, which has been called *leukosarcoma*, is true malignant neoplasia. As a rule it develops at a single site.

**Chloroma.**—This very rare tumor is of theoretical interest, because it forms a link between leukemia and tumor growth; it is a malignant tumor with a leukemic blood picture. Green tumors (*chloros*, green) are formed in the flat

bones of children and young adults, especially in the face and skull, where they may fill the orbit and push the eye forward. The sternum, spine, ribs and pelvic bones (red-marrow bones) are involved, and occasionally the long bones. There may be green tumors in the liver, kidneys, muscles and skin. The spleen and lymph nodes are often enlarged. The green color fades on exposure to air; the nature of the pigment is unknown. The bone-marrow of the long bones is filled with green tumor tissue. The tumors which can be detected clinically are under the periosteum, but it is probable that the primary growth is in the marrow, and that the periosteal tumors are secondary. The lesions consist of large non-granular cells similar to those of acute leukemia; there may be numerous granular myelocytes. The tissues (frozen sections) give the oxydase reaction. The tumors are much more invasive than the cellular collections of leukemia. The *blood* shows a picture of acute leukemia, although the total white cell count is not always increased. It used to be thought that the abnormal cells belonged to the lymphoid series, but it is now believed that they are myeloblasts. The distribution of the lesions in chloroma resembles that of multiple myeloma; the chief distinction between the two being that in myeloma the tumor cells do not enter the blood stream. Both are invariably fatal.

**The Nature of Leukemia.**—Leukemia is a disorderly, non-altruistic proliferation of myeloid or lymphoid cells, and on this account may be regarded as a neoplasm. A number of facts suggest that it may be inflammatory in nature. It resembles the leucocytosis and lymphocytosis of acute infections, fever may be a marked feature in acute leukemia, and a leukemia-like condition in fowls (leukosis) can be transmitted by the injection of a cell-free filtrate. In spite of these arguments we may repeat that leukemia is probably neoplastic in nature. Possibly it has a place in the dim borderland between inflammation and neoplasia. In leukosarcoma it has stepped across the borderline into frank malignancy. It is very difficult to draw any sharp line between lymphatic leukemia and lymphosarcoma. Myelogenous leukemia, chloroma, and multiple myeloma have much in common, including the appearance of Bence-Jones' protein in the urine in all three conditions. No one denies that lymphosarcoma, chloroma, and myeloma are true tumors. It is true that in leukemia there is seldom any marked degree of infiltration, but we must remember that the leucocyte is a peculiar cell in a class by itself. As Gulland remarks: "It is the gypsy among cells. The body for its own purpose forms traps to hold it—marrow, lymph glands, and so on—and encourages it to proliferate there, but it is always eager to be off on its own business." We would not expect such a cell to be markedly infiltrative.

**The Relation of Symptoms to Lesions.**—The clinical manifestations of the three main forms of leukemia naturally differ considerably. The age incidence of acute leukemia is in early life, being commonest in the first five years; myelogenous leukemia usually occurs between the ages of twenty-five and forty-five years, and lymphatic leukemia between the ages of forty-five and sixty years. The patient suffers from the usual weakness, dyspnea and palpitation of severe anemia, due to replacement of the erythroblastic tissue in the bone-marrow. There may be a fulness and dragging sensation in the abdomen due to the great splenic enlargement. This enlargement may sometimes be as great in the lymphatic as in the myelogenous form. The condition of the superficial lymph nodes is not always a reliable indication as to the presence



or absence of general lymphoid hyperplasia, for the deep nodes (abdominal and mediastinal) may be greatly enlarged though the superficial ones are barely palpable. Pain and tenderness of the sternum and more rarely of the long bones may be quite striking; this is caused by the hyperplastic-neoplastic process going on in the interior of the bone. Hemorrhages are common in all the varieties, particularly in the acute form, so that leukemia is classed as one of the "bleeding diseases." There may be hemorrhage from the nose, mouth, or bowel, or into the brain or retina. Bleeding gums and necrotic processes in the mouth, associated with fever and severe and progressive anemia are characteristic features of acute leukemia. The cause of the hemorrhage in leukemia is obscure. The coagulability of the blood is greatly decreased, but the reason for this is also unknown. Priapism may occur in the myelogenous form, due probably to engorgement of the penile cavernous tissue. Ascites, sometimes chylous, and chylous effusions in the chest may be due to pressure of enlarged glands on the thoracic duct. The basal metabolic rate is high owing probably to the increased metabolic activity of the great numbers of immature cells. The fever, which is most marked in acute leukemia, may be due to the same cause. A large amount of uric acid may appear in the urine owing to disintegration of nuclear material and liberation of nucleoproteins. The presence of Bence-Jones' protein in the urine is characteristic of bone-marrow lesions, being also found in chloroma and more particularly in multiple myeloma.

**Erythremia.**—This is a primary increase in the number of red blood cells, just as leukemia is a primary increase in the leucocytes. It is also known as polycythemia vera, polycythemia rubra, and Vaquez-Osler's disease. It must be distinguished from *erythrocytosis* or secondary polycythemia, a compensatory increase of red cells in conditions of insufficient oxygenation, *e. g.*, congenital heart disease, chronic valvular disease of the heart, emphysema, pulmonary arteriosclerosis, and residence at high altitudes. Erythrocytosis is a temporary condition, and corresponds to leucocytosis.

In true erythremia (polycythemia vera) there is an increase of the red cells irrespective of the needs of the body; they usually number from 7,000,000 to 10,000,000 per c.mm. In addition there is an increase in the volume of the blood, a true plethora, so that the total increase of red cells is greater than is indicated by the hemocytometer count. The blood becomes more viscid owing to the great number of red cells. The hemoglobin is increased to 125 or 150 per cent, and the color index is about 1. There is a moderate leucocytosis with a polymorphonuclear count of over 80 per cent. Occasional primitive red and white cells (normoblasts and myelocytes) may be seen in the film. The bone-marrow is markedly hyperplastic, the change being chiefly erythroblastic (normoblastic) in type, but with areas of myelocytic reaction. It also shows capillary thickening and marked subintimal and adventitial fibrosis of the arterioles. Splenomegaly is present, usually moderate, but sometimes marked.

It has been shown experimentally that imbalance of the vasomotor mechanism may exert a marked influence on the peripheral blood cell mass (Schafer). Removal of the carotid sinus and the cardio-aortic proprioceptive nerves in dogs is followed by pronounced persistent polycythemia, the red cell count being restored to normal by para-

vertebral sympathectomy. The mechanism involved is probably the production of an anoxemic condition of the bone-marrow due to vasoconstriction; this is known to stimulate the production of erythrocytes. These observations suggest at least a possible genesis of erythemia.

**The Relation of Symptoms to Lesions.**—The polycythemia appears to be due to a primary erythroblastic hyperplasia of the bone-marrow which may be neoplastic in character. A relationship to leukemia is suggested by the fact that occasional cases have changed from erythremia into leukemia of myelogenous type. A myeloblastosis in which the primary effect is on the erythroblastic tissue results in erythremia; when the primary effect is on leucoblastic tissue leukemia develops. The appearance of the patient is striking; the skin and mucous membrane of the mouth are red or bluish-red and the conjunctiva is blood-shot. The color is due to the increased number of red cells. At postmortem the visceral vessels are greatly distended owing to the increased blood volume; this is best seen in the mesenteric veins and these vessels may be thrombosed. Vertigo and sensations of fullness in the head are common; they are due to the great distention of the cerebral vessels, so that when the patient stoops he feels as if there was a rush of blood to the head. Hemorrhage from the mucous membranes or into the retina may occur on account of this vascular fullness. Peptic ulcer (usually duodenal) is a not uncommon complication. Possibly this is due to thrombosis of small vessels. The enlargement of the spleen may be regarded as a compensatory arrangement to deal with the increased number of red cells.

**Agranulocytosis.**—This condition, which has come much to the fore during recent years, is characterized by a remarkable disappearance of the granulocyte series of leucocytes from the blood and an accompanying drop in the total white cell count. It may not be possible to distinguish some cases from acute leukemia in the aleukemic stage. A differential point of value is that the platelet count is high in agranulocytosis but low in aleukemic leukemia. Most of the patients have been middle-aged women, and when accompanied, as is commonly the case, by necrotizing gangrenous lesions of the mouth involving the tonsils, gums, and even the bone of the jaw, it has in the past been nearly invariably fatal. The striking characteristic of the necrotic lesions of agranulocytosis is the almost entire absence of polymorphonuclears. There may be multiple ulcers of the stomach and intestine, and sometimes of the vulva. The association of leucopenia and destructive lesions of the mouth is known as agranulocytic angina. The condition is not a disease *sui generis*, but rather a symptom complex, an indication of the action of some powerful leucocidal poison, some destroyer of the bone-marrow, which may or may not be accompanied by severe infection of the mouth. Three groups of cases may be distinguished: (1) A primary form with fever, ulcerative mouth lesions, and agranulocytosis, so that leucocytes are absent from the necrotic ulcers. No definite cause such as a constant and specific microorganism can be found. (2) Malignant leucopenia of bacterial origin, as in pneumonia, osteomyelitis, etc. (3) Malignant leucopenia of toxic origin; benzol, antisyphilitic arsenical preparations, and certain analgesic and antipyretic drugs such as amidopyrine and the barbiturate series, *i. e.*, chemicals containing the benzene ring, may so depress the bone-

narrow that leucopenia results and bacterial infection of the mouth may develop in consequence. Should the patient continue to take the drug, as all too often happens, a fatal termination can hardly be avoided. Agranulocytosis, and especially agranulocytic angina, is a new disease, for the first case was reported by Schultz in 1922, and the steady increase in the number of cases corresponds with the increase in the consumption of drugs containing the benzene ring. Many of the patients display a hypersensitiveness to drugs, and probably this is a factor of great importance.

The *pathogenesis* of the second and third groups is easy to understand. That of the first group is much more obscure. It is known that certain pyogenic bacteria are capable of producing a leucocidin, a toxin specifically lethal for the leucocytes, the granular series in particular. *Staphylococcus aureus*, *Streptococcus hemolyticus*, and *Streptococcus viridans* are the most powerful members of this group. Dennis found that when these organisms, particularly *Streptococcus viridans*, were placed in celloidin capsules and inserted in the tissues, a diffusible toxin was produced which was powerfully leucocidal. When filtrates of the cultures in the capsules were mixed with leucocytes they caused disintegration of the polymorphonuclears, though the lymphocytes were unaffected. Pyogenic bacteria can produce agranulocytosis only when prevented from active penetration of the tissues, otherwise they merely excite leucocytosis. This suggests that some circumscribed focus of infection is present in the primary cases.

The *bone marrow* in the acute cases shows lack of maturation in the granular series of cells which therefore largely disappear, together with hyperplasia of the stem cells. The essence of the disease seems to be a maturation arrest affecting the granular leucocytes, so that they are unable to enter the circulation (poverty in the midst of plenty), a situation strictly comparable to that of pernicious anemia. In the more prolonged cases there may be hypoplasia of the myeloid tissue which contains large numbers of plasma cells and lymphocytes. In recovery there is a rapid change of stem cells into myelocytes and polymorphonuclears. In the neutropenia of overwhelming sepsis and arsphenamine poisoning there is not the same disappearance of adult granular cells from the marrow, and segmented forms can be seen.

The prognosis in the past has been extremely grave. This, however, has been greatly altered for the better by the introduction of the intramuscular use of pentose nucleotide (pentnucleotide), which acts as a specific stimulant to the leucoblastic tissue of the marrow. The recognition of the danger of using such drugs as amidopyrine and the barbiturates will undoubtedly change the prognosis still further.

**Primary Splenic Neutropenia.**—This condition, described by Wiseman and Doan in 1939, is characterized by marked neutropenia, splenomegaly and marrow hyperplasia. The white cell count may be extraordinarily low owing to disappearance of the neutrophils, in one case falling to .150 per c.mm. In a few hours after splenectomy the count may be increased 20 times. The condition is apparently a manifestation of hypersplenism, there being an accelerated destruction of the granular leucocytes by the reticulo-endothelial

cells of the spleen. It is permanently cured by splenectomy. The spleen is rich in highly phagocytic cells containing polymorphonuclear leucocytes and erythrocytes. There is often a hemolytic anemia and a diminution of platelets. The condition may therefore be compared to congenital hemolytic anemia and thrombocytopenic purpura, to which it is evidently related. "The reticulo-endothelial cells of the spleen when on a rampage of destruction may selectively choose as victim any *one* of the elements of marrow origin passing through this organ, but more often than not other innocent bystanding elements suffer likewise in some degree. Splenectomy always is followed by an increase in *all* circulating blood elements whenever applied in any one of these conditions" (Wiseman and Doan).

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## CHAPTER XXXI

### THE NERVOUS SYSTEM

#### GENERAL PATHOLOGY OF THE NERVOUS SYSTEM

**Descriptive Outline.**—In describing so complex a structure as the brain, method is all-important. Consideration must be given to the following: meninges, cerebrum (cortex, white matter, basal ganglia, and ventricles), mid-brain (including aqueduct, red nucleus and substantia nigra), pons and medulla (including fourth ventricle), cerebellum, base of brain, circle of Willis, and branches of middle cerebral artery. The average weight in the male is 1400 grams, in the female 1250 grams. There is a minimal amount of cerebrospinal fluid in the subarachnoid space, much more in the basal cisterns. The pia-arachnoid is glistening, translucent, and is stripped off readily without tearing the brain (decortication). The subarachnoid space may be distended with fluid in conditions of edema. The convolutions are rounded and the sulci of moderate size. In cerebral atrophy the convolutions become shrunken and the sulci wide and deep, whereas in increased intracranial pressure the convolutions are flattened and the sulci obliterated. Not only the size but also the lining of the ventricles must be noted; it becomes granular in general paresis. The substantia nigra is examined for loss of pigment in chronic encephalitis lethargica. The vessels at the base should be soft and free from atheroma.

The *microscopic description* includes neurones, neuroglia, and vessels. The neurone consists of a nerve cell and fiber. In the nerve cell consider the nucleus, nucleolus, Nissl granules, pigment, and the shape and outline of the cell. In the nerve fiber consider the axis cylinder, medullary sheath, and sheath of Schwann. In connection with the neuroglia attention must be paid to astrocytes, oligodendroglia, and microglia. Finally, the perivascular (Virchow-Robin) spaces must not be forgotten, and the vessels which they surround.

**The Neurone.**—The central nervous system consists of two main elements: (1) the neurones and (2) the interstitial tissue or neuroglia. These react to irritants and injuries in entirely different ways. It is necessary to understand these reactions before the study of the special pathology of the nervous system can be undertaken. The neurone, the essential unit of the whole system, consists of a nerve cell and nerve fiber. The nerve fiber is made up of three constituents, the axis cylinder or axon, the medullary or myelin sheath, and the neurolemma or nucleated sheath of Schwann. Within the central nervous system the fibers consist only of the first two elements; the sheath of Schwann is added when the fiber becomes peripheral.

**Wallerian Degeneration.**—When a nerve fiber is divided or when the cell from which it arises is killed, the *distal part* of the fiber shows the characteristic changes first described by Waller in 1850. The axis cylinder becomes fibrillated and disintegrates, the medullary sheath breaks up into droplets of myelin which can be stained black by Marchi's method, and the cells of the sheath of Schwann are converted

into phagocytes which remove the remnants of the medullary sheath and axis cylinder. These cells also play an essential part in regeneration, a process which will be studied when the healing of nerve is considered. As the sheath of Schwann is not present in the central nervous system it is evident that healing after injury cannot occur in the brain and spinal cord. The complete process of Wallerian degeneration is best studied in a peripheral nerve, but the axonal and medullary sheath changes take place in the central nervous system also and have proved of extreme value in the experimental study of the path of fibers and tracts owing to the ease with which the degenerating myelin can be stained. The *proximal part* of the divided fiber also shows changes. The medullary sheath degenerates up to the first node of Ranvier, and the nuclei of the sheath of Schwann multiply in this segment of the nerve, and help to bridge the gap between the two ends of the divided fiber in a way which will be described in connection with injuries to nerves. The nerve cell from which the fiber arises undergoes Nissl's degeneration (see below).

Wallerian degeneration readily occurs as the result of *avitaminosis*, for the health of the medullary sheath is dependent on vitamins, especially B<sub>1</sub>. There is, however, no activity on the part of the Schwann cells. When vitamin B<sub>2</sub> is withheld experimentally degeneration of the anterolateral and dorsal tracts of the cord occurs as well as myelin degeneration of the peripheral nerves.

A word may be devoted to the *staining methods* used for demonstrating the medullary sheath changes in a degenerating nerve. Osmic acid stains myelin black, because the peroxide of osmium of which it is composed is reduced by the fat, forming a black compound with it which is insoluble in xylol, so that the method can be used for paraffin sections. The distinction between the normal and degenerating myelin is achieved by *Marchi's method*, which depends on the principle of selective oxidation. Normal myelin is readily oxidized by degenerating myelin very slowly oxidized when kept in an oxidizing fluid such as a solution of potassium bichromate. When the material is then treated with osmic acid, the normal tissue remains unstained as it has been fully oxidized and is therefore unable to reduce the osmic acid. The degenerated myelin, on the other hand, is very slightly oxidized, so that it readily reduces the osmium peroxide with the formation of the characteristic black compound. By means of Marchi's method, degenerating fibers can be traced through the length and breadth of the central nervous system, and the method has been of the greatest value in the experimental study of the course of nerve paths within that system. It is evident that too long a time must not elapse between the date of the injury and the application of the staining method, for if all the myelin has been removed there is no use trying to stain it. The Marchi method is used for the first few weeks after an injury. After that time the *Weigert myelin sheath stain* must be employed. This is the converse of the Marchi method, for it stains normal myelin dark blue or black; the degenerated fibers remain unstained, as their myelin has disappeared. The tissue is first mordanted in potassium bichromate so as to render the myelin insoluble, and is then stained with hematoxylin. The Marchi method is mainly used by the physiologist, who employs the experimental method. The Weigert method is of special value to the pathologist in the study of degenerative lesions of the white matter of long standing, *e. g.*, *tabes dorsalis*, *disseminated sclerosis*, etc.

**Nissl's Degeneration.**—When a nerve cell is acted on by chemical or bacterial toxins it undergoes characteristic degenerative changes. Similar changes are seen in a cell when the nerve fiber which arises from it is injured; this variety is known as axonal degeneration. The same secondary changes in the cell occur as the result of alcoholic and other forms of neuritis. The cell becomes swollen and rounded, the nucleus becomes eccentric in position and may be situated at the extreme margin, and the Nissl granules in the cytoplasm disintegrate and disappear. (Figs. 422 and 423.) It is this condition, known as chromatolysis, to which the degeneration owes its name. It is evident from what has been said that Nissl's degeneration is complementary



FIG. 422.—Normal nerve cell showing processes, concave borders, Nissl granules, nucleus and nucleolus.  $\times 600$ .



FIG. 423.—Degenerated nerve cell: borders convex, loss of processes, Nissl granules and nucleus.  $\times 600$ .

to Wallerian degeneration. About three weeks after division of the nerve, regeneration begins, the granules reappear, and the cell body is restored to normal. These regenerative changes are not seen in the cells of the upper motor neurones, just as no regeneration occurs in the fibers of these neurones.

The *distinction between upper and lower motor neurone lesions* is one of the most fundamental in neuropathology. Upper motor neurone lesions affect any part of the pyramidal tract from the motor cells in the cortex to the termination of the fibers around the anterior horn cells of the cord or the motor nuclei of the cranial nerves. Lower motor neurone lesions involve the anterior horn cells and their fibers or the motor nuclei of the cranial nerves and their fibers. Lesions of



either the upper or lower neurone causes paralysis of muscles, but they can usually be readily distinguished from one another. The characteristics of *upper neurone lesions* are spasticity (increased muscle tone), exaggerated deep reflexes, and Babinski's sign (dorsiflexion of great toe on stimulation of sole of foot). *Lower motor neurone lesions* are characterized by flaccidity of the paralyzed muscles, loss of the deep reflexes, muscular atrophy and severe trophic disturbances, fibrillary twitchings in the affected muscles, and the reaction of degeneration in these muscles. The commonest example of an upper motor neurone lesion is afforded by a hemorrhage into the internal capsule which destroys the pyramidal tract fibers. Examples of lower motor lesions are poliomyelitis (infantile paralysis), transverse myelitis, and the ordinary form of facial paralysis.

**Pigmentary Changes.**—In elderly persons and in degenerative conditions many nerve cells come to contain yellow pigment granules, probably a lipochrome. This must not be confused with the melanin which normally gives the cells of the substantia nigra a dark color.

**Atrophy.**—There is marked general atrophy of the cerebral cortex in general paresis, Pick's convolutional atrophy and to a lesser degree in chronic alcoholism and senility. More localized atrophy may occur as the result of arteriosclerotic narrowing of the vessels. On account of the shrinkage of the brain there is widening of the subarachnoid space which is filled with fluid, and compensatory dilatation of the cerebral ventricles. In the atrophic areas the nerve cells are small and withered, and there may be an increase of yellow pigment in their cytoplasm.

**The Interstitial Tissue.**—The interstitial tissue of the central nervous system has long been known as the neuroglia. Glia means glue, and the neuroglia was regarded as a kind of putty which served the humble purpose of holding together the more noble neurones. The work of the Spanish school of neurohistologists, which Ramón y Cajal and del Río Hortega are the leaders, has changed all this, and their contributions form the most notable recent advance in our understanding of the structure and working of the central nervous system. In ordinary preparations the interstitial elements appear for the most part as naked nuclei, although staining with phosphotungstic acid-hematoxylin may demonstrate that many glial cells possess processes which give them a star-shaped appearance so that they are known as astrocytes. They may be distinguished from nerve cells by the fact that they do not possess a nucleolus. Gold and silver impregnation, however, gives an entirely different picture, and in place of naked nuclei we now see cells provided with a forest of fibers, which present quite as striking an appearance as the cells and fibers of the neurones. By the aid of these methods, which we owe very largely to the Spanish school, it is possible to distinguish three elements in the interstitial tissue: these are the *astrocytes*, the *oligodendroglia*, and the *microglia*. The first two are ectodermal in origin, and together make up the neuroglia. The third is mesodermal in origin and is unrelated to the neuroglia.

**Astrocytes.**—The best known cells of the neuroglia are the astrocytes. These are divided into protoplasmic and fibrous forms. The former have protoplasmic processes and are confined almost entirely to the cortical gray matter. The latter have fibrillary processes, and are found principally in the white matter but also form a dense layer in the most superficial part of the cortex immediately under the pia mater, where they constitute a "superficial limiting membrane." The astrocyte is a large cell with numerous processes, at least one of which is attached to a small vessel by a curious expansion to which the names of vascular foot plate, suction apparatus, and sucker foot have been applied. The neurones are everywhere separated from the vessels by a layer of astrocytes. The astrocytes are best demonstrated by Cajal's gold-sublimate method. (Fig. 424.)

Their *function* is certainly not merely that of support or glue. It has been suggested by those best qualified to express an opinion that



FIG. 424.—Gliosis (gold sublimate).  
× 315.

one or more of three functions may be ascribed to this tissue: (1) It may be an endocrine structure which pours an internal secretion into the blood, derangement of which may be responsible for some of the so-called functional nervous disorders; (2) it may have a nutritive function in relation to the neurones as suggested by the term suction apparatus; (3) it may serve to neutralize toxins circulating in the central nervous system and thus protect the delicate nerve cells. It is not possible to discuss here the reasons for these various views. The astrocyte plays an active part *in disease*. Hortega and Penfield have shown that the repair of wounds in the brain is due entirely to the activity of the astrocytes, which enlarge, multiply, and fill in the gap, just as fibroblasts do in other parts of the body. The gliosis seen

in general paresis and other chronic inflammations consists of astrocytes and their fibers. In experimental intoxications the perivascular astrocytes develop into amoeboid cells, the processes and sucker feet being much swollen at first and later becoming absorbed into the body of the cell. Finally, the astrocyte is the cell from which the great majority of gliomas (astrocytomas, glioblastomas) arise. The oligodendroglia rarely and the microglia apparently never take on neoplastic growth.

**Oligodendroglia.** This is the largest group of the interstitial cells, but the one about which the least is known. In ordinary sections they appear as naked nuclei arranged in rows between the nerve fibers in the white matter, and in the gray matter as satellites adhering to

the nerve cells. When stained by Hortega's silver carbonate method the cells, which are much smaller than the astrocytes, are seen to possess a small number of fine processes (*oligos*, few). (Fig. 425.)

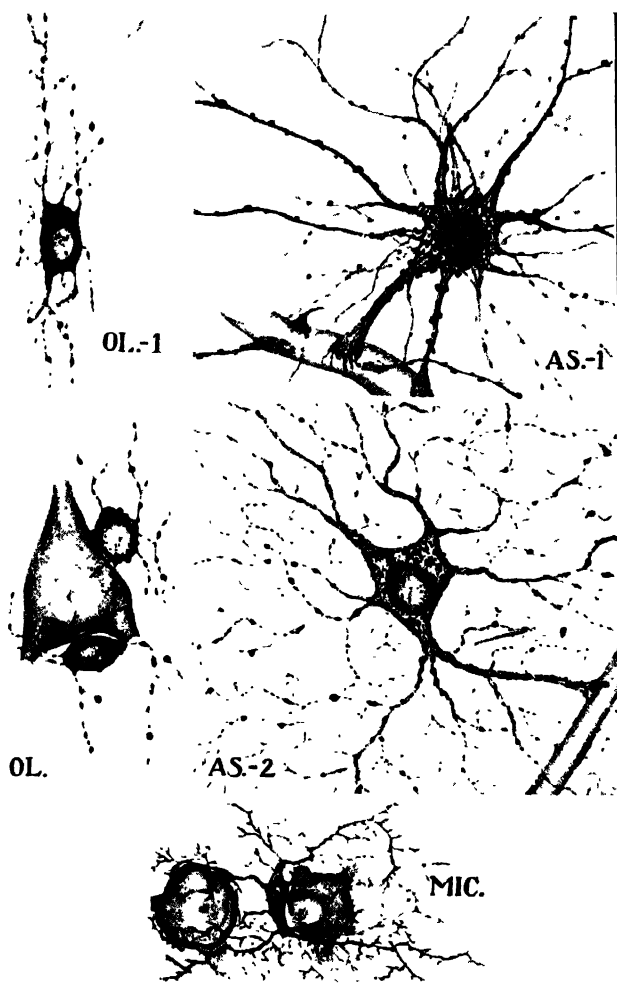


FIG. 425.—The interstitial cells of the central nervous system. AS.-1, Fibrous astrocyte with several perivascular feet on bloodvessel. AS.-2, Protoplasmic astrocyte showing numerous processes but no fibrils. OL.-1, Oligodendroglia. OL., Two oligodendroglia cells as perineuronal satellites around nerve cell in which nucleolus is distinctly shown. MIC., Microglia cells with numerous processes placed between and in contact with two nerve cells; in the latter the nucleolus can be distinguished. (Penfield, in Cowdry's *Special Cytology*, P. B. Hoeber, New York.)

The *function* of these cells is obscure. They seem to bear the same relation to the myelin sheath of the nerve fibers in the central nervous system as the cells of the sheath of Schwann do in the peripheral

nerves, so that they may have something to do with the preservation of the myelin. *In disease* they appear to play a part of no importance. They are evidently very sensitive to noxious agents, for they readily undergo acute swelling, becoming pale, vacuolated, and losing their processes. The cells are seldom seen in perfect form in human material, for they rapidly undergo autolysis after death.

**Microglia.**—The microglia differs fundamentally from the other two elements in being mesodermal in origin, while they originate from ectoderm. The cells are very small (hence the name), and are provided with numerous fine branching processes which are stained by the silver carbonate method. Some of them form satellites to the nerve cells. (Fig. 425.) The microglia is not present at birth, but invades the brain from the pia in the course of a few weeks. These cells may be regarded as forming part of the reticulo-endothelial system, for when studied in tissue cultures by vital staining they behave in exactly the same way.

The *function* of the microglia is phagocytic; the cells are indeed the phagocytes of the central nervous system. Under pathological conditions they develop into the rod cells of general paresis and the scavenger cells (also known as compound granular corpuscles, fat granule cells and Gitterzellen) seen in brain softening. The transformation of the quiescent microglial cell into the amœboid and phagocytic scavenger cell is a remarkable one. The cell body becomes swollen and rounded, the processes are thickened and then withdrawn into the cell, and the cytoplasm becomes filled with fat globules derived from the disintegrating myelin. The cells collect in enormous numbers at the site of injury, and then appear to carry the ingested myelin to the nearest vessels, into which they possibly discharge their content.

**Corpora Amylacea.**—These are small spherical hyaline bodies, sometimes displaying a concentric structure, which are seen in large numbers in the nervous system in old age, and may occur earlier as a result of degenerative diseases. It used to be thought that they arose from the medullary sheath of degenerating nerves or possibly from nerve cells, but recent work seems to indicate that they represent degenerated microglial cells, or in some cases they may be formed from the oligodendroglia.

### INTRACRANIAL HEMORRHAGE

Hemorrhage in the interior of the skull may come from the brain or the meninges; it may be cerebral or meningeal. In traumatic cases the two may be combined.

**Cerebral Hemorrhage.**—Hemorrhage into the brain may be *traumatic* or *spontaneous*. It is important to remember that a patient who has had a trauma to the head may nevertheless be suffering from a spontaneous hemorrhage. The hemorrhage may come first, causing him to fall, injure his head, even fracture his skull. This is particularly true when the hemorrhage is in the internal capsule.

**Traumatic Hemorrhage.**—Trauma may cause cerebral hemorrhage in two ways. (1) Hemorrhage is a more or less constant accompaniment of *laceration of the brain*. Fracture of the base or vault of the skull may be

present, but it is important to realize that large cortical hemorrhage may occur without fracture. *Contrecoup* hemorrhage, which is situated on the side opposite the site of trauma, usually occurs without fracture; it is caused by the brain being thrown forcibly against the opposite side of the skull. A large hemorrhage due to trauma is very rarely (perhaps never) in the internal capsule, such hemorrhage being spontaneous. (2) *Multiple punctate hemorrhages* in the basal ganglia and elsewhere may be caused by trauma. These are probably the result of a wave of cerebrospinal fluid which the blow on the head causes to pass from the subarachnoid space into the perivascular prolongations of that space, with forcible stretching of the fibrillary extensions from the vessel wall to the perivascular sheath. Great numbers of small ring hemorrhages are formed around the vessels in this way, and if the patient survives these may be followed by gliosis which may form the organic basis of many of the post-traumatic neuroses. Martland has suggested that the condition known to prize-fighters as "punch-drunk" may be due to a wave of cerebrospinal fluid injuring the vessels; many old fighters develop corpus striatum symptoms (paralysis agitans, etc.).

**Spontaneous Hemorrhage.**- This may take two very different forms, the *punctate* and the *massive*. The latter is the ordinary form of cerebral hemorrhage.

*Punctate hemorrhage* occurs as the result of infections and intoxications, as well as in the bleeding diseases. It may therefore be found in the infective fevers, septicemia, epidemic encephalitis, and bacterial endocarditis, in carbon monoxide poisoning and arsphenamine poisoning, and in pernicious anemia, leukemia, and purpura hæmorrhagica. In all of these conditions there is damage to the vessel wall. The hemorrhages are very small and very numerous. They are commoner in the white matter and basal ganglia than in the cortex. Each hemorrhage surrounds a small vessel, but often there is a narrow necrotic zone between the vessel and the hemorrhage, and there may be necrosis without hemorrhage. It would appear, therefore, that the necrosis is the primary condition and the hemorrhage secondary.

*Massive hemorrhage* constitutes what is commonly known as *apoplexy*. It usually occurs in middle-aged and elderly men with high blood-pressure and arterial degeneration. Owing to the hypertension the heart is enlarged, and it has been said that "the large heart breaks the weak vessels." Hemorrhage may occur in the absence of hypertension provided the atheromatous degeneration is very marked. The opinion is gaining ground that apoplectic hemorrhage is not merely a question of a bloodvessel bursting, as an aneurism of the aorta might burst. It takes place into soil which has been prepared by vascular thrombosis, occlusion, or perhaps even by spasm. As a result of the ischemia a focal encephalomalacia is produced, and it would appear that such softening is an essential precursor to rupture of a vessel. Syphilis is not a direct cause of cerebral hemorrhage, for it produces a uniform thickening, not a localized weakening, of the

vessel wall. Indirectly it may play a part by causing occlusion and thrombosis; this produces an area of softening into which hemorrhage may occur. An infected embolus lodging in one of the cerebral vessels may give rise to a mycotic aneurism, which on rupturing may cause a massive hemorrhage. So-called miliary aneurisms may be present. These are false aneurisms, the blood having broken through a weak spot in the wall and produced a localized bulging of the adventitia; this may give way and be a source of hemorrhage. An occasional cause of hemorrhage is rupture of a congenital aneurism on the circle of Willis or one of its branches; this usually leads to subarachnoid hemorrhage, but the blood may make its way into the brain substance. Such an aneurism should be looked for in cerebral hemorrhage in a young person. Epidemic encephalitis may cause massive hemorrhage, but this is rare and should never be suspected except during an epidemic. In some cases no cause for the hemorrhage can be suggested.

In *hypertensive encephalopathy* three types of lesion may be encountered: (1) edema, causing such symptoms of increased intracranial pressure as headache, nausea, vomiting, dulness, etc.; (2) multiple miliary destructive lesions (ischemic), causing a wide variety of symptoms such as vertigo, transient hemiplegias and aphasias, convulsions, etc.; and (3) massive hemorrhage into larger areas of softening.

The common site of massive hemorrhage is the internal capsule and lenticular nucleus. The small arteries to the basal ganglia come directly off the middle cerebral, so that the pressure is not "stepped down" by continuous branching as in the case of the cortical branches. The lenticulostriate artery was long ago called "the artery of cerebral hemorrhage." The next most common site is the white matter of the frontal lobe, the hemorrhage coming from the anterior cerebral artery. Next come the pons and cerebellum. Spontaneous hemorrhage in the cerebral cortex is rare. Hemorrhage in the basal ganglia may extend inward, and more rarely outward. When it passes inward it may penetrate the caudate nucleus and rupture into the lateral ventricle. (Fig. 426.) About 40 per cent of fatal capsular hemorrhages rupture into the lateral ventricle before death. Pontine hemorrhages almost invariably rupture into the fourth ventricle. Spontaneous intracerebral hemorrhage only very rarely ruptures outward into the subarachnoid space. The blood passes through the aqueduct and fills the entire ventricular system, passing thence to the subarachnoid space *via* the foramina in the roof of the fourth ventricle and filling the cisterns at the base of the brain. The original hemorrhage may be into the ventricles, usually from the anterior cerebral which supplies the tip of the caudate nucleus.

A clot is formed at the site of the hemorrhage, and this may be surrounded by petechial hemorrhages, caused probably by the sudden disturbance of pressure. The brain tissue in which the hemorrhage has occurred is torn up and completely disintegrated. The clot becomes softened and the destroyed brain substance liquefied, so that if the patient lives the hemorrhage is replaced by a cyst containing

yellow or milky fluid. The surrounding tissue is stained yellow, and this discoloration may persist for a long time. *Microscopically* there is great destruction of neurones. The nerve cells are degenerated



FIG. 426.—Cerebral hemorrhage. The hemorrhage has started in the internal capsule, passed inward through the optic thalamus, and ruptured into the lateral ventricle.

and the medullary sheaths are broken up into droplets of myelin; presently the entire neurone disappears. In the case of the motor paths the degenerated fibers can be traced down through the brain stem (Fig. 427) into the cord. Two elements of the interstitial tissue, the astrocytes and the microglia, show marked activity. The *microglia* gives rise to large numbers of scavenger cells, which take up the myelin droplets and pigment granules, carrying them to the nearest vessels and perhaps discharging them into the lumen. The *neuroglia cells* (astrocytes) proliferate and form abundant fibers, so that a small cyst may be obliterated, while a larger cyst is shut off from the surrounding tissue by a glial zone. Granules of blood pigment indicate for many years the hemorrhagic origin of the cyst.



FIG. 427.—Hemiplegia: degeneration of right crossed and left direct pyramidal tract.

**The Relation of Symptoms to Lesions.**—Depending on the size of the hemorrhage, the patient with apoplexy either feels faint or loses consciousness. He may fall as though struck to the ground (*plexis*, to strike down), but sudden death is rarely due to cerebral hemorrhage unless it be into the ventricles or the medulla. The immediate loss of consciousness is due to the sudden cerebral anemia caused by compression of the capillaries by the hemorrhage, and the coma into which the patient may pass is to be attributed to the rapidly developing edema. It is the compression of the vital centers in the medulla by the edema which is the usual cause of death. The condition of the *cerebrospinal fluid* is of help in the diagnosis. In hemorrhage into the ventricles a large amount of blood is present in the fluid. When the hemorrhage does not communicate with the ventricles the fluid is at first normal, but in the course of three days it assumes a yellow tinge owing to blood pigment having seeped through into the ventricles. This is not found in any of the other comatose states which simulate cerebral hemorrhage.

The *focal lesions* depend on the site of the hemorrhage. When this is in the *internal capsule* there is paralysis of the face, arm, and leg of the opposite side. This paralysis, of course, is of the upper motor neurone type, with spasticity, exaggeration of the deep reflexes, Babinski's sign, etc., owing to removal of the cerebral influences which inhibit the normal tone of the lower motor neurone. At first, however, there is flaccidity with loss of deep reflexes instead of spasticity, owing to shock produced by the hemorrhage. The motor fibers occupy the anterior two-thirds of the posterior limb of the capsule, while the sensory fibers pass up in the posterior limb, so that if the hemorrhage extends sufficiently far back there will also be hemianesthesia of the paralyzed side. Just behind the capsule pass the fibers of the optic radiation, and if this is involved there will be homonymous hemianopia (blindness in one-half of the field of vision). *Hemorrhage into the ventricles* is characterized by sudden loss of consciousness, loss of all the reflexes, and a rapid rise of temperature; the condition soon proves fatal. In *pontine hemorrhage* hyperpyrexia is again present, and the pupils are extremely contracted (pin-point pupils) owing to interruption of the pupil-dilating fibers. Hemiplegia will be present if the pyramidal tract is involved. *Cerebellar hemorrhage* is accompanied by persistent vomiting, nystagmus and deviation of the eyes to the side of the lesion, and a tendency to fall to that side. As the pyramidal tract is not involved there is no paralysis.

**Meningeal Hemorrhage.**—Meningeal hemorrhage may be *extradural*, *subdural*, or *subarachnoid*.

1. **Extradural Hemorrhage.**—This is commonly called *middle meningeal hemorrhage*, being due to injury to the middle meningeal artery from fracture of the lower part of the parietal bone or the squamous portion of the temporal bone. It is caused by a direct blow; the elastic recoil of the skull separates the dura from the bone, and the spaces become filled with blood. A large clot is formed outside the dura over the vertex and this presses on the brain. (Fig. 428.) Prompt operation with ligation of the bleeding vessel is needed, otherwise the patient will die from compression of the brain. The *clinical picture* is highly characteristic. There may be brief loss of consciousness owing to the blow. This is followed by a *lucid interval* of some hours, at the end of which time symptoms of compression appear owing to the gradual accumulation of blood between the skull and the brain. There is no blood in the cerebrospinal fluid. A useful localizing sign is a fixed dilated pupil on the *same side* as the lesion, due probably to herniation of the hippocampal uncus with pressure on the third nerve as it crosses



PLATE XXVII



**Subdural Hemorrhage**

In addition to the blood clot on the brain and the inner surface of the dura there is diffuse staining of the cerebrum.



the greater wing of the sphenoid. There may also be conjugate deviation of the eyes to the opposite side due to irritation of the oculomotor center in the second frontal convolution.

2. **Subdural Hemorrhage.**—Subdural hemorrhage (Plate XXVII) may be regarded as venous, just as extradural hemorrhage is arterial in origin. The condition, which is at least 4 times as common as extradural hemorrhage, is of great importance, because the life of the patient depends on a correct diagnosis and this is easily missed. It is customary to recognize a traumatic and a spontaneous form, but it is becoming doubtful if the latter is more than a myth, for the traumatic factor in the etiology is often slight and easily overlooked. The cause is a blow in the frontal or occipital region (*e. g.*, knocking the head against a shelf or door), which injures the cerebral veins passing into the sagittal sinus. As there are no septa to localize the extravasated blood, it



FIG. 428.—Extradural hemorrhage.

may spread from the frontal to the occipital pole and from the sagittal sinus to the Sylvian fissure. The symptoms may not come on for weeks or even months after the injury. This is explained by the unique subsequent behavior of the clot. This is not absorbed as it would be in other serous sacs, for the subdural space is closed and without lymphatics. The clot becomes liquefied and surrounded by a mesothelial membrane, so that a cyst is formed which separates the dura from the brain. Into this cyst cerebrospinal fluid is drawn by the osmotic pressure of the blood, so that the tension in the cyst continually increases, with corresponding pressure on the brain. At the site of a subdural hematoma, therefore, the dura is lined by a dirty-green, gelatinous membrane which is easily detached, and the cyst contains dark green, thin fluid under pressure. *Pachymeningitis hæmorrhagica interna* is a term which has long been applied to the supposedly spontaneous form in which a membrane containing

great numbers of large blood spaces is found on the inner surface of the dura. Hemorrhage is supposed to occur at intervals from these giant capillaries, but they are also present in traumatic cases.

The *symptoms* are mental confusion and somnolence coming on weeks or even months after some trivial trauma to the head. Temporal tenderness is a valuable sign. Most of the cases are men over forty years with lessened elasticity of the skull and more fragile cerebral veins. Rather remarkably, the spinal pressure is not increased, but the fluid may be yellow (xanthochromia) due to histiocytes traversing the arachnoid barrier and giving up their blood pigment to the cerebrospinal fluid in the subarachnoid space. As might be expected, surgical treatment is highly satisfactory.

*Intracranial hemorrhage of the newborn* is a variety of subdural hemorrhage. It is a common cause of death in the new-born. The child is cyanosed, the respirations difficult, the pulse slow, the fontanelle bulging, and there may be twitching movements. Death may occur in a few hours or in the course of a day or two. If the child survives, paralytic and mental symptoms may develop later. The hemorrhage is due to tears in the tentorium cerebelli or the falx cerebri or to injury to the cerebral veins passing from the cortex across the subdural space into the superior longitudinal sinus. These injuries are produced by the severe molding of the head which occurs at birth, and not necessarily by the use of instruments. The hemorrhage is largely supratentorial and often bilateral. It is commoner in the premature than in the full-term infant owing to immaturity of the fibers of the dural septa. The arachnoid is often torn, so that blood is found in the cerebrospinal fluid. Lumbar puncture is of great use in doubtful cases. The gravity of the condition depends not merely on the extent of the lesion, but on whether the child suffers from a hemorrhagic diathesis which interferes with the clotting of the blood. This is due to a low prothrombin content of the blood, and the condition can be treated by injections of vitamin K, or prevented by giving the vitamin to the mother before delivery.

3. **Subarachnoid Hemorrhage.**—This may be traumatic or spontaneous. (1) *Traumatic hemorrhage* is likely to occur in all lacerations of the brain, so that blood will appear in the spinal fluid. The presence of blood in the subarachnoid space may irritate the cells of the arachnoid and cause blockage of the arachnoid villi through which the cerebrospinal fluid is absorbed into the venous blood sinuses. As the fluid cannot escape in the normal way it may collect in pools and cause pressure atrophy of the underlying cortex. It is possible that this may partly explain the puzzling post-traumatic neuroses and psychoses. The presence of pressure atrophy can be demonstrated in the living patient by means of encephalography or injection of air into the subarachnoid space.

(2) *Spontaneous subarachnoid hemorrhage* is a fairly common condition. The blood may leak into the subarachnoid space from a cerebral hemorrhage, or the subarachnoid hemorrhage may be primary. The common lesion found is atheroma of the cerebral vessels or the arteries

at the base of the brain. This may or may not be associated with aneurismal dilatation. In young persons the usual finding is a ruptured congenital aneurism on the circle of Willis (Fig. 429), or on one of its branches such as the anterior or middle cerebral. The little aneurism is covered by blood clot and is easily missed unless specially looked for. Sometimes the blood may pass into the brain, giving a picture easily mistaken for that of ordinary cerebral hemorrhage. The condition, which should always be considered in intracranial hemorrhage in a young person, is described more fully in connection with intracranial aneurisms. These aneurismal cases are usually fatal. There is another group of cases which usually recover and are probably due to some rather mild infection, some meningo-encephalitis, which especially attacks the vessels. They occur in groups or little epidemics, a fact which serves to strengthen the idea that they are infections, although of this there is no direct proof.

The *symptoms* are characteristic. The very sudden onset of severe headache and stiffness of the neck may suggest meningitis. Milder cases are mistaken for epidemic encephalitis. In the aneurism cases there may be partial recovery after the initial onset, only to be followed a few days later by a second more violent and often fatal attack.

There is apparently at first a partial break with some leakage and the formation of a false aneurism, followed later by complete rupture into the subarachnoid space. The cerebrospinal fluid contains a large amount of blood, which can be distinguished from accidental blood, due to the puncture by the fact that there is some hemolysis with yellow coloration (xanthochromia) of the fluid after centrifugation. Both albuminuria (often massive) and glycosuria are frequent.



FIG. 429.—Congenital aneurism of circle of Willis with hemorrhage.

## VASCULAR LESIONS

**Arterial Obstruction.**—A cerebral artery may be obstructed partially or completely. *Partial obstruction* may be due to atheroma, obliterative arteriosclerosis, or syphilitic endarteritis. The resulting anoxia may lead to degeneration of the sensitive neurones and proliferation of the more resistant neuroglia. Such gliosis is seen in old age, and is most marked in senile dementia. The alternation of minute foci of

cystic softening and glial scars may give the cortical surface a granulated appearance.

If attention is focussed on atheromatous patches in the larger arteries at the base of the brain it will often happen that there is no apparent relationship between the clinical picture and the vascular lesions. This is not true if the smaller vessels within the brain substance be examined. Here the characteristic lesion is a peculiar change which has been called obliterative arteriosclerosis (Scheinker). Its distinguishing feature is extreme thickening of the intima due to cellular (fibroblastic) proliferation and hyperplasia of the ground substance with corresponding narrowing of the lumen. Later the cells may degenerate and be replaced by a network of connective tissue fibers. The lesion can be distinguished from the hyperplastic arteriolosclerosis of hypertension in that in the latter the media and adventitia are thickened as well as the intima and there is an absence of intimal cellular proliferation.

*Complete obstruction* is due to embolism or thrombosis. (1) *Cerebral embolism* usually affects the middle cerebral artery on the left side, due probably to the more direct origin of the left carotid artery from the aorta. The clot which forms the embolus may arise in any of the usual sites (vegetation on mitral or aortic valve, thrombus in left auricular appendix or on an atheromatous ulcer of the aorta, etc.). If the clot is septic, an abscess or a mycotic aneurism may be formed, and the latter may rupture with fatal results. Usually it is aseptic, and the result is cerebral softening. Cone and Barrera have shown that when an aseptic infarct is produced in a dog the area and the overlying meninges become flooded with polymorphonuclears in eight hours with a maximum at forty-eight hours. The leucocytes may reach the cerebrospinal fluid in small or large numbers by the perivascular spaces or by direct invasion of the subarachnoid space or ventricles. The process, which is comparable to the leucocytosis in infarction of the myocardium, may be mistaken clinically for abscess or meningitis owing to the pus cells in the spinal fluid. The area of softening depends partly on the site of the obstruction and partly on the collateral circulation. If, as is usually the case, the middle cerebral is blocked before the branches to the basal ganglia are given off, both that region and the cortical area are deprived of blood and may undergo softening. There is a good collateral circulation in the cortex, so that the softening is often confined to the basal ganglia, but if the vessels are narrowed by arteriosclerosis or if the heart's action is weak, the collateral circulation is insufficient and the cortex may suffer severely. The motor fibers passing down through the internal capsule are destroyed, so that the opposite half of the body is paralyzed. If the obstruction is above the point where the arteries to the basal ganglia are given off, the lesion will be entirely cortical. (2) *Thrombosis* is usually due to atheroma or syphilis of the artery; atheroma is the common cause after middle life, and syphilis at an earlier age. The arteries most often the seat of thrombosis are the middle cerebral, posterior cerebral, and basilar.

Thrombosis of the basilar artery causes softening of the pons. The symptoms develop more slowly than in embolism, but the effect is the same.

**Cerebral Softening.**—When an area of the brain (or spinal cord) is deprived of its blood supply it undergoes necrosis and in the course of a few days becomes liquefied and converted into a creamy material. (Fig. 430.) In the experimental animal temporary arrest of the circulation for five minutes causes necrosis and softening of the cerebral



FIG. 430.—Large area of softening in the lenticular nucleus with cyst formation, due to vascular occlusion.

cortex; if the arrest is maintained for over seven minutes there is complete destruction and liquefaction of the brain substance (Weinberger *et al.*). The color is usually pale, but in the course of time becomes yellow owing to blood pigment and the lipoid liberated from breaking down myelin. In exceptional cases it is red on account of marked congestion. The sequence of events is similar to that which occurs in hemorrhage. As liquefaction proceeds a cyst is formed with clear or milky contents and a yellow margin. The neuroglia proliferates and forms a limiting zone around the cavity. (Fig. 431.) When the

cortex is involved a cyst is formed beneath the meninges, or there may simply be atrophy of the convolutions with depression of the affected area.

The *microscopic changes* involve both the neurones and the interstitial tissue. A smear of the liquefied material shows at first granules and globules of lipoid, the remains of cells and fibers, and large numbers of scavenger cells. In sections of the affected area there is complete necrosis and loss of all structure. Secondary (Wallerian) degeneration can be traced down the course of the motor fibers through pons, medulla, and cord, the droplets of myelin being demonstrated by the Marchi method. At a later date Weigert's myelin sheath stain shows



FIG. 431.—Gliosis at margin of softened area.  $\times 300$ .



FIG. 432.—Scavenger cells of the brain (Hortega cells) filled with lipoid. These cells are derived from the microglia.  $\times 1000$ .

complete disappearance of the fibers, whose place is occupied by proliferated neuroglia. A zone of gliosis is seen around the wall of the cyst. But the most characteristic feature of a recent softening is the presence of enormous numbers of large pale scavenger cells derived from the microglia and filled with lipoid globules taken up from the disintegrating myelin. (Fig. 432.) These cells are known by a variety of names such as compound granular corpuscles, fat granule cells Gitterzellen (lattice cells), and Hortega cells on account of the demonstration by del Rio Hortega that they are microglial in origin. Frozen sections stained for fat with Scharlach show in a beautiful manner the lipoid character of the cell contents. The walls of the vessels are



infiltrated with these cells, which seem to be discharging their contents into the lumen.

**Venous Obstruction.**—This is caused by thrombosis of the venous sinuses. Not infrequently the cerebral thrombosis is part of a general venous thrombosis. In other cases it is of local infective origin, as in sinus thrombophlebitis due to spread of infection from the middle ear, nose, etc. The superior longitudinal sinus is most often affected. In severe cases there may be a remarkable dilatation of the superficial veins which become completely thrombosed, so that the surface of the brain seems to be covered with dark worms.

**Intracranial Aneurisms.**—These aneurisms are nearly always extra-cerebral, for they are situated on the circle of Willis or its main branches. Aneurismal dilatations in the brain substance are seldom true aneurisms. There are three main types of intracranial aneurisms. In their order of frequency these are the *congenital*, the *mycotic*, and the *arteriosclerotic*. Aneurisms due to syphilis are practically non-existent, though this is not usually realized.

1. **Congenital Aneurism.**—These aneurisms, which may be multiple, form small swellings on the vessels of the circle of Willis, the middle cerebral, anterior cerebral, and anterior communicating. (Fig. 429.) They are usually found in young people, and are known as berry aneurisms. The most striking peculiarity of the aneurism is that in every case it is situated at the bifurcation of the vessel. At this point there is often an absence of the muscular tissue of the middle coat in normal persons, which may be looked on as a congenital vascular malformation or defect. The same localized medial defect is found in the congenital aneurism, the wall of which is formed by greatly thickened intima, with complete absence of media and internal elastic lamina. There may be other vascular anomalies, *e. g.*, coarctation of the aorta. Glynn does not believe that there is any proof that congenital medial defects are the cause of the aneurisms, for he finds such defects as common among controls as in cases of aneurism (80 per cent in each group). He points out that in the vessels of the circle of Willis all the elastic fibers are concentrated in the internal elastic lamina, not distributed throughout the media and adventitia as in other arteries. For this reason a patch of atheroma may destroy all the elastic tissue and thus produce an aneurism. Atheroma is almost constantly present in these aneurisms, but has been regarded as secondary rather than primary. If this interpretation is correct, berry aneurisms must be regarded as atheromatous, not congenital, in origin. Rupture of the aneurism leads to hemorrhage into the subarachnoid space which is usually fatal. If the aneurism is on the anterior cerebral or the anterior communicating artery and therefore wedged in between the frontal lobes, it may rupture into the brain substance. The same is true of the middle cerebral. These cases are easily mistaken in the autopsy room for ordinary cerebral hemorrhage, the aneurism being lost in the hemorrhage and readily overlooked.

2. **Mycotic Aneurism.**—An infected embolus, usually from a vegetation on a heart valve, lodges in the middle or anterior cerebral artery and sets up an acute arteritis. This weakens the wall so much that a small mycotic aneurism is formed, which is certain to rupture unless the patient dies before that happens.

3. **Atheromatous Aneurism.**—This form usually occurs over the age of fifty years. If, however, the so-called congenital aneurisms are admitted to be of atheromatous origin, the lesion is common between the ages of twenty and thirty. An atheromatous patch in the intima is pressed by the blood against the media producing atrophy and consequent dilatation. A saccular aneurism is thus formed.

### DISTURBANCES OF CEREBROSPINAL FLUID CIRCULATION

**Hydrocephalus.**—Hydrocephalus or water on the brain is a condition in which the cerebrospinal fluid collects inside (and sometimes outside) the ventricles, so that these cavities become greatly dilated with an accompanying pressure atrophy of the cerebral tissue. The cerebrospinal fluid is secreted by the choroid plexus of the lateral and other ventricles, passes along the aqueduct of Sylvius to the fourth ventricle and escapes through the foramina in the roof of that ventricle to enter the basal cisterns of the subarachnoid space. From there it flows upward through the narrows between the brain stem and the incisura in the tentorium, to expand again into the shallow lake of the cerebral portion of the subarachnoid space. It also passes down from the basal cisterns into the spinal canal, where it can be withdrawn by lumbar puncture. The *normal pressure* is 7 to 9 mm. of mercury or 110 to 130 mm. of water. The fluid is absorbed into the large venous sinuses, especially the superior longitudinal sinus, by way of the arachnoid villi, which are diverticula of the subarachnoid space that project into the lumen of the sinuses. The Pacchionian bodies are hypertrophied villi which are only found in adult life. It is evident that if the fluid is unable to escape from the ventricles absorption is impossible, if it cannot pass from the basal cisterns to the cortical subarachnoid space absorption will be impaired, and there may be local interference with absorption if the arachnoid villi and Pacchionian bodies are blocked. The obstruction may occur at three points: (1) in the aqueduct, (2) in the roof of the fourth ventricle, and (3) around the mesencephalon where it passes through the narrow opening in the tentorium. The first two cause *internal hydrocephalus*, the third causes *communicating hydrocephalus*, the ventricles being in open communication with the basal cisterns and the spinal canal. All three are obstructing.

The ordinary hydrocephalus of children is due to obstruction either in the roof of the fourth ventricle or in the aqueduct. The exact cause of the obstruction is not certain, but it is probable that adhesions due to a mild meningitis are the most frequent cause of obstruction in the roof of the ventricle. The aqueduct may be occluded by a delicate veil-like membrane which is probably the result of a developmental

defect, but may in some cases be due to slight intra-uterine inflammation. Congenital hydrocephalus is due to obstruction of the aqueduct. A rare cause is the so-called *Arnold-Chiari malformation*, a congenital deformity of the hind-brain in which the brain stem is displaced through the foramen magnum, plugging of which prevents absorption of the cerebrospinal fluid. Hydrocephalus may complicate meningitis or brain tumors. Tuberculous meningitis, the lesions of which are essentially basilar, is always accompanied by dilatation of the ventricles, due to the formation of a plastic exudate on the roof of the fourth ventricle with blockage of the foramina of Magendie and Luschka. Hydrocephalus is a common accompaniment of brain tumors and is the chief cause of such classical symptoms as headache, vomiting, and optic neuritis. It may be produced in a variety of ways. (1) A glioma of the fourth ventricle or mid-brain may cause complete obstruction of the aqueduct. (2) A tumor above the tentorium may press the cerebrum down so as to wedge the brain stem into the opening in the tentorium, thus producing obstruction to the flow of fluid from the basal cisterns to the cortical subarachnoid space and so preventing absorption. (3) If the brain is pressed upward against the vault of the skull the subarachnoid space will be obliterated and again absorption will be interfered with. It is small wonder, then, that hydrocephalus is a common accompaniment of brain tumor.

The greatest degree of hydrocephalus is seen in young children, in whom the head is still capable of enlargement. The enlargement may be enormous, with wide separation of the cranial bones, islands of bone in a sea of membrane. The little wizened face is surmounted by the huge dome-like cranium, which toward the end becomes little more than a bag of jelly. The degree of dilatation of the ventricles varies from the slightest to the most extreme. (Fig. 433.) In the latter the cerebral tissue is reduced to a mere shell from pressure atrophy, but the subtentorial structures remain wonderfully intact. This is one of the saddest features of the disease, for the mental deterioration may be complete, yet the intact vital centers in the medulla allow the child to continue its miserable and vegetative existence.

**Cerebral Edema.**—Edema of the brain is a condition in which fluid collects in the brain substance, particularly in the perivascular and perineuronal spaces. This must be sharply distinguished from accumulation of fluid in the subarachnoid space. The two conditions may be associated, but the mechanism by which they are produced is quite different. The edema may be due to general or local causes. *General causes* such as cardiac or renal edema may cause cerebral edema. In nephritis and particularly in uremia the edema may be marked. Chronic alcoholism is often associated with a "wet brain." *Local causes* are hemorrhage, inflammation, and tumor of the brain. Any such focus is sufficient to disturb the intracranial circulation sufficiently to allow fluid to pass from the vessels into the soft tissues of the brain. The edematous brain is pale, moist, and softer than normal. The distinction between gray and white matter is not well

marked. The convolutions are swollen and the sulci narrowed. Moisture exudes from the cut surface. When the edema is due to general causes there is likely to be an excess of fluid in the subarachnoid space. When the cause is local this space may be empty owing to pressure of the brain from below.



FIG. 433. -Hydrocephalus. The ventricles are moderately dilated.

**Traumatic Edema.**—The edema which follows trauma is of extreme practical importance on account of the disturbance which it causes in the circulation of the cerebrospinal fluid. The best example of this type of edema is seen in fracture of the skull. It is not the injury to the bone which is of importance but the laceration of the brain, as a result of which local edema and swelling rapidly develop. If the swelling is marked and persistent the brain tends to be pushed up or down, depending on the site of the hemorrhage. If it is pushed up against the skull, the subarachnoid space over the vertex is obliterated so that no absorption of fluid can occur. If it is pushed down, the opening in the tentorium is plugged so that the fluid cannot pass from the basal cisterns to the upper subarachnoid space. In both cases the result is the same—a great accumulation of fluid at the base of the brain with increasing pressure on the vital centers in the medulla, as indicated by slowing of the pulse and respiration. This clinical picture of compression is usually attributed to “medullary edema,” but it is evident that the effects are not due to a local edema of the medulla but to disturbance of the cerebrospinal fluid circulation.

There is another way in which the absorption of the cerebrospinal fluid may be interfered with. Various lesions of the arachnoid villi and Pacchionian bodies (which are merely hypertrophied villi) may prevent absorption and cause the fluid to accumulate over the cortex in the subarachnoid space (Winkelman and Fay). The fluid may be dammed back in the ventricles; indeed a marked degree of hydrocephalus can be produced experimentally by injecting lamp-black into the basal cisterns and in this way blocking the villi. Aplasia or hypoplasia of the villi may cause congenital hydrocephalus. There may be fibrosis of the villi in general paresis, uremia, and chronic alcoholism. Blocking of the villi by exudate occurs in acute and tuberculous meningitis and as the result of hemorrhage into the subarachnoid space. It is therefore always well to remove as much blood as possible by means of lumbar puncture. As the result of the defective absorption large pools of fluid collect over the cortex, obscuring the convolutions. The subarachnoid space is continued into the brain in the form of the perivascular sheath, so that the cerebral tissue is everywhere permeated by cerebrospinal fluid. An excess of fluid on the surface will often find its way into the interior, thus explaining the "wet brain" of uremia, chronic alcoholism, etc.

It is easy to understand the relief which is afforded by reducing the intracranial pressure in these cases. This may be done by lumbar puncture, or by dehydrating the brain by introducing magnesium sulphate into the bowel, or giving 50 per cent sugar solution intravenously. The high osmotic pressure draws water from the blood into the bowel, and at the same time from the brain into the blood. The dehydrated brain shrinks in volume, and there is a marked fall of intracranial pressure.

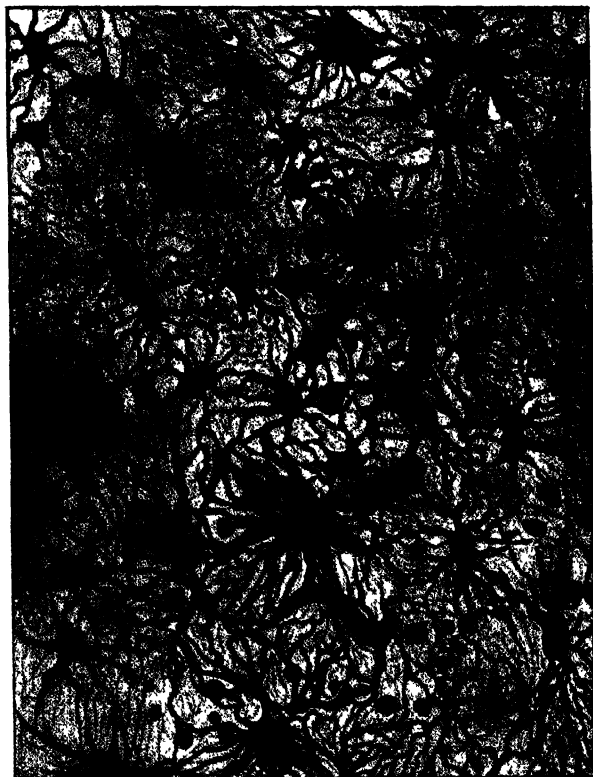
**Epilepsy.**--There is no generally recognized pathology for *idiopathic epilepsy*, but recent observations have shown, both in the operating room and by means of encephalography (injection of air into the subarachnoid space by lumbar puncture followed by radiography), that in the convulsive states there are dilatations of the subarachnoid pathways with corresponding atrophy of the underlying convolutions. Similar changes are seen in *post-traumatic epilepsy*. The pia-arachnoid is thick and opaque. There may be dilatation of the ventricles. The collections of fluid and atrophy of the corresponding convolutions are readily seen on the operating table, but not in the postmortem room. The frontal and parietal lobes are the regions most often affected. No one can say for certain if the atrophy is primary and the collection of fluid secondary, or if the excess of fluid is the cause of the atrophy. The atrophy does not correspond with the vascular distribution, but is limited to the cerebrospinal fluid pathways. It seems probable that the initial lesion may be an arachnoiditis, the effect of which is to block the villi and to divide the subarachnoid space into areas in which the excess of fluid is confined. Whether this is really an important factor in the causation of idiopathic epilepsy remains to be seen.

## INJURIES OF THE BRAIN AND SPINAL CORD

**Laceration.**—Varying degrees of laceration are common results of head injury. This may occur with or without fracture of the skull. Fracture, indeed, seems to act as a safety valve for the brain, as in a case which I observed of a child who fell on his head from a height of two stories and sustained a fracture of the skull which extended from the base over the vertex to the base on the other side, but suffered no permanent ill effects. Often the laceration is most marked on the side opposite to that on which the blow is struck, the condition known as *contrecoup*. Contrecoup injury, which is commonly seen on the under surface of the frontal lobes and the temporal and occipital poles, may be more or less severe than the lesion at the site of the original injury. Occasionally the only hemorrhage found is in the pons or mid-brain due to impact of the brain stem against the basi-occiput. When the patient dies months or years later, cortical defects may be seen at the summits of the convolutions. The end result is a worm-eaten scarred area of cortex to which are attached the overlying arachnoid and dura. There is demyelination and neuroglial scarring of the underlying white matter. These lesions, often small and easily overlooked, may be yellowish-brown in color due to the presence of old blood pigment. The acutely injured brain is swollen, a swelling usually attributed to edema, although some workers question this explanation. Petechial hemorrhages are common. Under the microscope they take the form of so-called ring hemorrhages, a ring of red blood cells around a central necrotic area. The lesions are really in the nature of hemorrhagic infarcts rather than true hemorrhages; blockage of a small vessel leads to necrosis, with diapedesis of red cells into the necrotic zone.

The *neuroglial reaction* to trauma has attracted much attention, both in the experimental animal and in man. All three glial elements, microglia, oligodendroglia and astrocytes, share in the changes. The *microglia* reacts to local destruction and disintegration of tissue. Transition forms of microglia are found within a few hours of laceration, but fully formed compound granular corpuscles, the scavenger cells of the central nervous system, only appear after three or four days; they remain as long as products of disintegration are present. The *oligodendroglia* reacts immediately after injury with enlargement and vacuolization of the cells; in a few hours there is acute swelling which persists for weeks, especially about the local injury. Acute swelling of the oligodendroglia is one of the commonest and least specific of glial reactions. It is found in every patient dying in coma. The *astrocytes* undergo regressive changes with the development of amœboid forms in the first few days after injury. In the zone nearest the injury there is complete destruction, but beyond this zone there is active proliferation, with cellular mitosis and the formation of a dense feltwork of fibrils. (Plate XXVIII.) This gliosis persists indefinitely in the neighborhood of the lesion. The damaged part of the brain shrinks, and fluid collects in the subarachnoid space. A vascular woof of sclerotic tissue

## PLATE XXVIII



Proliferation of astrocytes as the result of injury to the brain. The astrocytes are attached to the walls of the bloodvessels by long processes. Stained with gold chloride.





is formed which is adherent above to the meninges and below to the general vaso-astral framework of the brain (Penfield). The scar undergoes contraction over a period of months and years, exerting a constant pull not only locally but on the whole framework of the brain. This is probably one of the most important causes of *traumatic epilepsy* of the Jacksonian type, which may come on a number of years after the original injury. If the injured tissue can be removed soon after the trauma, formation of the vascular connective tissue is prevented, and the likelihood of subsequent epilepsy greatly diminished.

**Concussion.**—This is a transient state following head injury, of instantaneous onset, with purely paralytic symptoms, no sign of cerebral damage, and always followed by amnesia for the actual moment of the accident. As the result of a blow on the head, which as a rule does not produce a fracture, the patient instantaneously loses consciousness, and at the same time passes into a condition of profound shock. The face is pale and the body covered with a cold sweat, the temperature is subnormal, the pulse imperceptible, and the respiration almost suspended. The patient soon recovers consciousness, and as reaction sets in the temperature rises and the pulse becomes bounding. In some cases an unpleasant sequel is a marked degree of irritability, a condition of “cerebral irritation” which may last for a long time.

If a patient suffering from concussion should die, the autopsy findings are inconclusive. There may be laceration of the brain especially on the under surface of the frontal and temporal lobes, with hemorrhage into the subarachnoid space. These lesions can have nothing to do with the sudden loss of consciousness and development of shock. Petechial hemorrhages may be scattered through the brain, owing probably to a wave of cerebrospinal fluid which the blow causes to travel from the subarachnoid space into the perivascular sheaths and the perineuronal spaces. The sudden anemia produced by this perivascular wave in the cerebral cortex would account for the loss of consciousness, while a similar condition in the medulla would produce the phenomena of shock. As the vessels become filled again the stage of reaction would set in. The subsequent irritability is probably due to injury produced by the sudden violent distention of the perivascular sheaths, of which the petechial hemorrhages are the visible indication, and this may be followed by gliosis. The allied subject of “punch drunk” has already been discussed in connection with traumatic cerebral hemorrhage.

**Compression. Increased Intracranial Pressure.**—The brain is confined within a rigid bony box and contains the most sensitive cells in the body. An increase of pressure is therefore of great importance, and may give rise to the clinical picture known as compression. The four chief causes of compression are hemorrhage, abscess, tumor, and edema. Edema may complicate any of the other three, and is the cause of compression (in conjunction with hydrocephalus) in laceration of the brain and fracture of the skull. At the site of the pressure the vessels are emptied of blood, and it is the medullary anemia thus

produced which renders the condition so dangerous. The fluid is driven out of the cerebral subarachnoid space into the spinal canal, thus giving the brain a little more elbow-room, but the relief is only temporary. The dura is tense and the convolutions flattened so that the sulci can hardly be detected. In the traumatic cases where the brain is forced up against the skull, the subarachnoid space may be empty when the dura is incised. In general cerebral edema and in cases where the cerebrospinal fluid eliminating mechanism is blocked (arachnoid villi and Pacchionian bodies) there may be an abundance of fluid over the cortex.

**Symptoms.**—The symptoms of compression are the same no matter what the original cause may be. The higher centers suffer first, so that the mind is dulled and the patient gradually sinks into coma. Pressure on the motor centers may first cause convulsive movements, followed later by paralysis. The vital centers in the medulla are first stimulated and then depressed, so that the pulse, respirations, and blood-pressure are all affected. It is not too much to say that with the exception of motor paralysis nearly all the really important symptoms of intracranial lesions are due to increase of the intracranial pressure. This is particularly true of brain tumor. The classical symptoms of that condition—headache, vomiting, and optic neuritis—are late manifestations of increased pressure. Nearly all the surgeon's troubles in the operating room are due to this cause, and every effort must be made to combat the increase. Particularly in traumatic cases, repeated lumbar puncture and dehydration of the brain by the intravenous use of hypertonic salt solution or the administration of magnesium sulphate are of much greater value in reducing the pressure than a decompression operation.

**Spinal Cord Injuries.**—The spinal cord is most frequently injured by fracture or dislocation of the vertebræ. Hemorrhage, wounds, etc., are much less common causes. At the site of the lesion there is the same disintegration, softening, and liquefaction as occurs in the brain. The immediate result of a severe injury is motor and sensory paralysis below the lesion and loss of the organic reflexes. If the lesion involves the cervical enlargement, the upper limbs will show a lower motor neurone type of paralysis owing to destruction of the anterior horn cells, while the lower limbs will show an upper motor neurone paralysis from destruction of the pyramidal tracts. It is extremely interesting to examine sections taken above and below the lesion and stained with Weigert's myelin sheath stain. If sufficient time has elapsed for degeneration of the medullary sheaths to occur, all the motor tracts *below* the lesion will be degenerated while the sensory tracts are intact, but *above* the lesion the motor tracts are intact while the sensory ones are degenerated.

*Hematomyelia* or hemorrhage into the cord is nearly always due to trauma. There is first softening of the cord, followed later by hemorrhage. The hemorrhage may extend longitudinally in the gray matter of the cord, sometimes involving the greater part of the cord. In the rare cases which recover the blood may be replaced by glial tissue, giving a lesion very similar to syringomyelia.

## INTRACRANIAL SUPPURATION

Suppuration within the cranial cavity may take the form of *extradural abscess*, *abscess of the brain*, and *sinus thrombophlebitis*. Acute meningitis is also a suppurative condition, but is more conveniently considered under a separate heading.

**Extradural Abscess.**—The infection spreads from the skull as the result of osteomyelitis of the cranium, a compound fracture, middle-ear disease, or frontal sinus infection. A collection of pus is formed external to the dura, and as that membrane offers a stout barrier to the spread of infection, the abscess may remain localized for a considerable time. The scalp over the inflamed area of bone becomes swollen and edematous, forming what is known as *Pott's puffy tumor*, a condition described by Percival Pott in 1760.



FIG. 434.—Single metastatic brain abscess in the frontal lobe secondary to an abscess of the lung. The right ventricle is dilated.

**Abscess of the Brain.**—The infection may spread from a local focus or may be carried from a distance by the blood stream. The common *local focus* is middle-ear suppuration. It may also result from infection of the frontal and nasal sinuses, from osteomyelitis of the skull, or from a compound fracture. Infection from the middle ear may spread up through the tegmen tympani, in which case the surface of the bone is eroded, or by the veins, when no external lesion can be seen either on the bone or the cerebral surface. *Distant infection* most often comes from a septic focus in the lung, usually bronchiectasis; sometimes there is empyema. It is probable that infection spreads from the lung to the brain by the vertebral system of veins (see page 258). This would explain the fact that there are no abscesses in other organs. The abscess is often single, the common site being the white matter of the frontal lobe. (Fig. 434.)

The abscess cavity is filled with pus in which there may be staphylococci, streptococci, or pneumococci. *Bacillus pyocyaneus* is often present, giving the pus a greenish color. The common site in middle-ear cases is the temporo-sphenoidal lobe, sometimes the cerebellum. The latter is much the more serious because of the frequency of meningitis, probably due to the depth of the cerebellar folia. When the infection comes from the frontal and nasal sinuses the frontal lobe is involved. A well-formed capsule is produced at the end of three weeks by fibroblasts in the adventitia of vessels. It is only after the formation of this capsule that an operation can be undertaken with hope of success. The best results are those obtained in abscess secondary to middle ear infection, the worst in cases secondary to lung abscess. It is remarkable how silent a brain abscess may be for a considerable time, especially if it is in the temporo-sphenoidal lobe. The temperature may be normal, the pulse is slow (abnormally so), and there may be very little leucocytosis. The cerebrospinal fluid is usually normal, apart from increased pressure, but if the abscess approaches the surface polymorphonuclears may appear in the fluid, due to seepage of toxic material into the subarachnoid space. An encapsulated abscess may remain quiescent for many months, but eventually it will rupture into a ventricle or reach the surface and set up a fatal meningitis.

**Sinus Thrombophlebitis.**—Infection reaches the venous sinuses of the dura mater by spread from some neighboring focus. The wall of the sinus becomes inflamed (phlebitis), and thrombosis follows as a matter of course. The *lateral sinus* is infected from the middle ear and mastoid, so that this is the vessel most often involved. The *superior longitudinal sinus* is infected from erysipelas and other septic conditions of the scalp. The *cavernous sinus* is infected from septic foci in the nose, face, orbit, and sphenoidal air sinus; carbuncle of the face is especially dangerous in this respect.

The thrombosis tends to spread from one sinus to another, and from the lateral sinus down the jugular vein, which can be felt as a hard and tender cord. The infection may spread outward, causing meningitis or cerebral abscess. The great danger, however, is the softening and liquefaction which occur in the infected thrombus. At any moment a piece of the softened clot may be dislodged, carried by the jugular vein to the right side of the heart, and thence to the lungs where it is arrested. The inevitable result is the formation of a pulmonary abscess, followed later by pyæmia. For this reason ligation of the jugular vein must be done before any direct attack upon an infected lateral sinus can be attempted.

The *clinical course* of sinus thrombophlebitis is very different from that of cerebral abscess. In the former it is stormy and tempestuous compared with the calm and peace of the latter. High fever, rigors, and chills are common, owing to the continual discharge of septic material into the blood stream.

## MENINGITIS

Infection may reach the meninges by the blood stream, from the brain, or from neighboring foci of infection in the middle ear, nasopharynx, accessory nasal sinuses, etc. Meningitis may complicate fracture of the base of the skull, particularly the anterior cranial fossa with involvement of the nasal fossæ and ethmoidal sinuses. In such cases the fatal infection may come from infected sinuses through the fracture line many years after the accident (Linell and Robinson). Almost any pathogenic organism may cause meningitis and even fungi have been known to do so, but there are only four common ones; these are the *meningococcus*, *streptococcus*, *pneumococcus*, and *tubercle bacillus*. The first three are pyogenic and cause purulent inflammation, so that the pathological changes are practically identical.

**Meningococcal Meningitis.**—This is the commonest form of meningitis. The disease is usually sporadic, but may become epidemic. For this reason it is known as epidemic cerebrospinal meningitis. The epidemiology is quite different from that of an ordinary infectious fever, for there is seldom more than one case in a family, and it is difficult to trace the contagion. The explanation is that the receptivity of the throat is high, while that of the meninges is low. There are always far more carriers than patients, and a carrier epidemic precedes and accompanies a case epidemic.

The *mode of infection* of the meninges is a matter of doubt. The disease is certainly spread from one person to another as a throat infection, as can be readily shown by taking swabs of the throats of a community during an epidemic. The difficulty is to decide by what route the meningococcus passes from the nasopharynx to the meninges. It may possibly spread through the lymphatics in the cribriform plate of the ethmoid and thus reach the subarachnoid space, but neither the organisms nor any sign of inflammation can be found in the ethmoid in fatal cases. It seems more likely that infection is by the bloodstream, for the meningococci can be found in the blood in about one-third of the early cases; sometimes, indeed, they are confined to the blood and never reach the meninges (meningococcal septicemia). It may be that the meninges are infected primarily from the blood, but it is difficult to explain the fact that in fulminant cases where the patient dies within twenty-four hours the blood and the fluid in the ventricles contain meningococci, yet the meninges are normal. It appears more likely that a metastatic focus is set up in the choroid plexus, from which the microorganisms are poured into the ventricles. First a choroiditis and then an ependymitis is produced, the cocci living on the ependymal lining of the ventricles, which is an epithelial structure like the lining of the nasopharynx. The flow of fluid carries pus and bacteria into the basal cisterns and down the spinal canal as well as to a varying extent up into the cerebral subarachnoid space. In infants, especially those brought up on the bottle, the brain is very soft, so that the sulci and cerebral subarachnoid space

are easily closed by the increased pressure, and the pus collects entirely in the basal cisterns, giving the posterior basic type of meningitis seen only in infants.

**Lesions.**—The brain is covered with a purulent exudate, confined to the subarachnoid space and therefore most abundant in the sulci. (Fig. 435.) The meningeal vessels are greatly dilated. The exudate on the surface of the cerebrum is most marked in the frontal and parietal regions, but the bulk of the exudate is to be found at the base, where it fills the interpeduncular space, passes forward along the optic nerves, backward into the great cisterns and upward along the middle and anterior cerebral arteries. In the spinal canal the exudate is largely confined to the posterior surface of the cord, an effect of gravity. The ventricles are moderately dilated and filled with turbid fluid, the choroid plexus is hyperemic, and the lining of the ventricles roughened.



FIG. 435.—Acute meningococcus meningitis. The meningeal vessels are greatly dilated. Scattered over the surface are large opaque areas of purulent exudate.

*Microscopically* the subarachnoid space is filled with a purulent exudate consisting of polymorphonuclear leucocytes with a few lymphocytes and large mononuclear phagocytes. (Fig. 436.) Fibrin is seldom marked. The vessels are greatly distended and there may be small hemorrhages. Meningococci are present both inside and outside the leucocytes. The brain and cord are not affected, although the exudate may penetrate the perivascular sheaths for a little distance. The only place where there is any inflammation is under the ependyma and in the choroid plexus.

The rest of the body shows little change, for the meningococcus has difficulty in establishing itself in the tissues, although it flourishes on the surface of the upper respiratory tract and in the ventricles and subarachnoid space. The nasopharynx shows congestion, edema, and

an infiltration with lymphocytes and plasma cells. In rare cases the meningococcus may cause endocarditis, pericarditis, arthritis, adrenal hemorrhage, etc.

**Cerebrospinal Fluid.** Lumbar puncture shows the pressure to be raised owing to a marked increase in the amount of fluid formed. The fluid is turbid, but in the earliest stage it may be almost clear. The protein content is high, above 0.3 per cent and sometimes as high as 0.8 per cent. The sugar is diminished and may be absent, owing to the fermentative action of the meningococcus. The film shows the cells to be polymorphonuclears, but as recovery sets in their place is gradually taken by large mononuclear phagocytes (macrophages) and finally by lymphocytes. The meningococci are usually intracellular, but some may be extracellular. They are Gram-negative diplococci, bean-shaped and indistinguishable in smears from the gonococcus. They are seldom numerous and sometimes none can be found. In such a case one should not wait for the result of a culture, but administer anti-meningococcal serum at once. A purulent fluid in which no organisms can be found is almost certainly meningococcal. When culturing the fluid, at least a cubic centimeter should be used; it is useless to take a mere loopful. When a case has been treated for some time with intrathecal injection of serum and sulphonamide drugs, the fluid may remain turbid and full of pus cells though the bacteria disappear. This is due to an aseptic meningitis caused by the treatment. The result of culture rather than the gross appearance of the fluid is the true measure of the progress of the case.

#### The Relation of Symptoms of Lesions.—

The prognosis in meningococcal meningitis is much better than that in the pneumococcal and streptococcal forms. In severe cases there may be a hemorrhagic rash on the skin and mucous membranes. This is a septicemic manifestation, due to embolic plugging of the capillaries. Most of the cerebral symptoms, such as headache and vomiting, are due to increased intracranial pressure. Stiffness and retraction of the neck, the most characteristic part of the clinical picture, is caused by irritation at the posterior part of the base of the brain. It reaches its most extreme degree in the posterior basic meningitis of infants where the retraction may be so great that the head may actually touch the back, a condition of opisthotonos. Strabismus (squint) and diplopia (double vision) may be present due to involvement of the third, fourth, and sixth nerves at the base of the brain. The heightened intracranial pressure is due partly to an increased outpouring of fluid, partly to interference with the normal absorption from the cerebral subarachnoid space. This interference is caused by blockage of the eliminating apparatus (arachnoid villi and Pacchionian bodies) by the purulent exudate; the accumulation in the basal cisterns which tends to push the brain up against the roof of the skull probably plays a part. Lumbar puncture, and



FIG. 436. — Acute meningitis. The subarachnoid space is packed with inflammatory cells.  $\times 160$ .

still better cisternal puncture, will help to relieve this state of affairs. If the fluid is not absorbed it will accumulate in the ventricles which become dilated, but a true internal hydrocephalus due to blocking of the openings in the roof of the fourth ventricle is not common in adults. In infants it is a frequent and fatal complication, the great compressibility of the very soft brain of the infant being the most important factor.

**Meningococcal Septicemia.**—In every case of meningococcal meningitis there is probably an element of septicemia, but the term meningococcal septicemia is usually reserved for those cases in which there is a blood infection without a corresponding infection of the meninges. It is an extrameningeal meningococcal infection. Meningitis may sometimes develop after the septicemia has been in progress for a number of weeks; this is called meningitis tarda. The course of meningococcal septicemia varies enormously. The fulminating cases may be incredibly rapid, and in these the infection may be so heavy that large numbers of meningococci can be seen in the blood smears. As Herrick remarks: "No other infection so quickly slays." In other cases the infections may go on for weeks and even months, blood cultures being repeatedly positive. In the more severe septicemic cases a hemorrhagic rash is likely to be present.

**Other Forms of Suppurative Meningitis.**—*Pneumococcal meningitis* may be primary or secondary to infection in the middle ear, nasal sinuses or lung. The disease is very acute and usually fatal. The morbid anatomy is the same as that of meningococcal meningitis. The purulent cerebrospinal fluid contains large numbers of pneumococci, so that the diagnosis can readily be made from a smear. The fibrinogen is much increased, and the fluid may even clot spontaneously. *Streptococcal meningitis* is usually secondary to middle ear or sinus infection, but occasionally it may be primary. It has the same bad prognosis as pneumococcal meningitis. This prognosis, together with that of pneumococcal meningitis, has been greatly improved since the introduction of the sulphonamide drugs. The organism may be *Streptococcus hemolyticus*, *Streptococcus viridans* or *Streptococcus mucosus*. The last-named usually comes from the ear, causes the formation of a characteristically sticky mucoid exudate, and nearly always kills the patient. The morbid anatomy and the condition of the cerebrospinal fluid are the same as in the other two forms of acute meningitis. Streptococci are usually present in large numbers in the fluid. *Staphylococcal meningitis* is rare, and the organisms are present in very small numbers. *Influenza bacillus meningitis*, better called Pfeiffer's bacillus meningitis, is the fifth commonest form in America, although much less common in Britain. It is suppurative, commonest in children, and very fatal. Typhoid and paratyphoid bacilli and *Bacillus coli* are occasional causes of meningitis. Still more rare are *Bacillus pyocyaneus*, *Bacillus anthracis*, *Bacillus mallei*, Friedländer's pneumobacillus, *Micrococcus catarrhalis*, actinomyces and a streptothrix.

**Meningitis Sympathica.**—This is a non-bacterial inflammatory reaction in the cerebrospinal fluid, an aseptic meningitis. There is an increase in the amount of fluid and of protein, a marked increase of polymorphonuclear leucocytes which may be several thousand in number, turbidity of the fluid, but no bacteria. Stiffness of the neck and other signs of meningitis may be present. The meningeal inflammation is due to the action of toxins from a neighboring focus of infection, of which the most important are brain abscess and suppuration in the middle ear and the accessory sinuses of the skull. The differentiation from ordinary acute meningitis is made by culture.

**Meningism.**—This is a name given to a condition usually in children, in which the symptoms simulate meningitis but no evidence of inflammation is found. The blood chlorides are very labile in childhood. They may fall in lobar pneumonia, after attacks of vomiting and diarrhea, or owing to drinking large amounts of water in high fever. There is an accompanying fall in cerebrospinal fluid chlorides, but it may be less rapid. As a result of this lag there is an outpouring of water into the subarachnoid space (due to the lowered



osmotic tension of the blood), and a heightening of intracranial pressure with symptoms suggestive of meningitis but at once relieved by lumbar puncture. The only abnormalities in the fluid are high pressure and low chlorides.

**Tuberculous Meningitis.**—Tuberculous infection of the meninges may be primary (in the sense that it is the first active lesion to manifest itself), or it may be part of a general miliary tuberculosis. The latter is invariably fatal, the former usually so but recovery is possible. In England 30 per cent of the cases are due to the bovine type of tubercle bacillus. The infection reaches the brain by the blood stream, and it is usually believed that the meninges are primarily involved. It can

be shown experimentally, however, that the meninges are very resistant to blood infection, even when large numbers of tubercle bacilli are injected into the carotid



FIG. 437.—Small tuberculous lesion of the brain discharging into the subarachnoid space. Several giant cells can be seen.



FIG. 438.—Tuberculous lesion in the brain rupturing into a blood vessel. Giant cells can be seen in the lumen of the vessel.

artery. On the other hand, they are readily infected when the injection is made directly into the subarachnoid space. Rich has shown that in most cases of tuberculous meningitis it is possible to demonstrate a tuberculous lesion in the brain, the choroid plexus, and even the meninges, and this lesion he regards as the primary source of the meningeal infection. The lesions are often multiple, but they may be no larger than a pea, so that the brain has to be cut into very thin slices if they are to be demonstrated. When one of these lesions is sufficiently superficial to discharge bacilli into the subarachnoid space or the ventricles, heavy infection of the meninges at once results. (Fig. 437.) The lesion may open into a

bloodvessel, causing general miliary tuberculosis (Fig. 438), or the Pacchionian bodies may be infected from the subarachnoid space and the bacilli pass in this way into the superior longitudinal sinus. Other workers do not agree with Rich, and believe that the meninges are infected from the blood stream. Beres and Meltzer examined 28 cases of tuberculous meningitis. In only 6 were there cortical tubercles which might have caused the meningitis, and in 11 there were tubercles in the choroid plexus.

**Lesions.** The type of lesion varies with the massiveness of the infection. If the dose is small the principal lesion is the miliary tubercle, but if it is large there may be an abundant non-specific exudative reaction with the formation of a creamy or greenish somewhat gelatin-



FIG. 439.—Tuberculous meningitis. The exudate covers base of brain.



FIG. 440.—Tuberculous granular ependymitis.

ous exudate at the base of the brain extending from the chiasma in front to the cerebellum behind, filling up the spaces (Fig. 439) and glueing together the surfaces. The tubercles are covered up by this exudate, but they can usually be seen on the upper surface of the cerebellum, on the velum interpositum, and along the line of the vessels as they pass up to the cortex. Sometimes almost no exudate or tubercles can be detected unless a very careful examination be made of the base of the brain with a hand lens. In these cases it is difficult to understand why the patient should have died. The convolutions are flattened and the sulci narrowed owing to the hydrocephalus which is nearly always present, and which is caused by the thick exudate over the roof of the fourth ventricle. The ependymal lining of the dilated ventricles is

roughened and granular ependymitis resembling that seen in cerebral syphilis is not uncommon. (Fig. 440.) When the brain is hardened and cut into very thin slices it is often possible to demonstrate small tuberculous lesions in the superficial part of the cortex or in the wall of the ventricle. Sometimes these lesions may be in the cord instead of the brain.

*Microscopically* the picture is a mixed one, partly tuberculous and partly inflammatory in nature. The tubercles seen with the naked eye consist of the familiar epithelioid cells and lymphocytes, but there is a remarkable absence of giant cells. In the primary tuberculous lesions of the brain, on the other hand, giant cells are numerous. The center of the tubercle is necrotic. The epithelioid cells may be arranged diffusely in the subarachnoid space, so that there is danger of not recognizing the tuberculous nature of the condition, but the presence of necrosis is highly characteristic. Tubercle bacilli can be seen in appropriately stained sections. When the reaction is more acute the subarachnoid space is filled with lymphocytes, plasma cells, and polymorphonuclears, but here again patches of necrosis indicate the nature of the process. The walls of the vessels are thickened and infiltrated with inflammatory cells. The *brain* is remarkably free from inflammatory lesions, but in places the infection may extend for a short distance into the cortex. The primary focus in the brain shows a typical picture of tuberculosis with giant-cell formation. Tuberculous necrotic foci can often be found in the choroid plexus and velum interpositum.

**Cerebrospinal Fluid.**—The diagnosis is made by lumbar puncture, so that the changes in the spinal fluid are of great importance. The clinical picture in poliomyelitis, epidemic encephalitis, and a deep brain abscess may closely resemble that of tuberculous meningitis, and unfortunately the spinal fluid findings are quite similar, but there are slight though important differences. The pressure is raised, and the fluid is clear or opalescent, almost never turbid. When allowed to stand a fine *web of fibrin* forms. This is very characteristic of tuberculous meningitis and is never seen in encephalitis and brain abscess, but a web sometimes forms in poliomyelitis and syphilitic meningitis. The *protein* is increased to a greater degree in tuberculous meningitis than in the other three (0.1 to 0.3 per cent). The *sugar* is decreased and sometimes disappears; in poliomyelitis and brain abscess it is normal, and in encephalitis it may be above normal (0.07 to 0.09 per cent). Estimation of sugar is therefore of great use in distinguishing between these easily confused conditions. The *chlorides* are low, below 0.65 per cent (normal: 0.72 to 0.75 per cent). This is the most valuable of all the chemical tests, for no other condition gives a really low reading. In exceptional cases the chlorides may be normal. The *cells* average from 50 to 200 per c.mm. (normal: 5 or less, though in children it may be higher). The cell count is usually below 50 in encephalitis and brain abscess, but in poliomyelitis it may be similar to tuberculous meningitis. The predominant cell is the lymphocyte, but in acute reactions, especially in children, there may be as many polymorphonuclears as lymphocytes. The demonstration of the *tubercle bacillus* is the conclusive proof of the nature of the condition. Both the web and the centrifuged deposit should be examined.

**The Relation of Symptoms to Lesions.** Paralysis of the cranial motor nerves, especially the oculomotor, may be caused by the exudate at the base of the brain, so that ptosis (drooping of the upper lid), squint, and diplopia are common. Stiffness and retraction of the neck are symptoms common to any meningeal irritation involving the base of the brain and the upper spinal

meninges. Cortical irritation may lead to spasms and convulsions. The acute hydrocephalus which is of such constant occurrence is responsible for symptoms of compression terminating in coma.

**Tuberculoma.**—This is a rather rare slow-growing circumscribed tuberculous lesion, often multiple, usually occurring in children, and easily mistaken for a tumor of the brain. It may become as large as a walnut. (Fig. 441.) It generally forms a firm spherical mass, but softening may sometimes occur with the formation of a tuberculous abscess. *Microscopically* the center is caseous, with epithelioid and giant cells at the margin. The prognosis is bad, for operative interference is nearly always followed by tuberculous meningitis or general miliary tuberculosis.

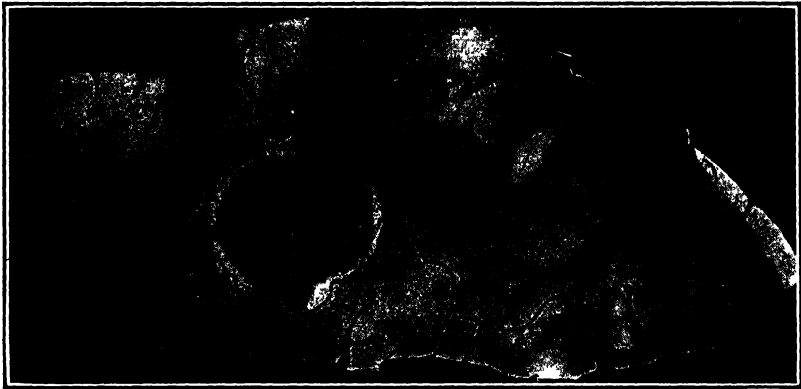


FIG. 441.—Tuberculoma of the brain.

**Tuberculoma en Plaque.**—Tuberculoma en plaque is a very rare tuberculous lesion occurring only in adults. There is a tuberculous meningo-encephalitis of very chronic character, with the formation of a flat plaque on the surface of the fronto-parietal cortex. The symptoms are those of tumor, *i. e.*, headache, vomiting and Jacksonian epilepsy, with the addition of fever.

**Torula Meningitis.**—This is a very rare condition due to torula infection, a yeast belonging to the group Blastomycetes. The cerebral lesion is a meningo-encephalitis, and the infection is secondary to a lesion in the lung or elsewhere. The lesions may simulate those of tuberculosis, consisting of epithelioid cells and giant cells, but the characteristic feature is the presence of large numbers of yeast-like cells.

**Lymphocytic Choriomeningitis.**—Under this heading are placed cases of acute but mild meningitis, characterized by a remarkable lymphocytosis. The cell count may be as high as 600 per c.mm. The fluid is sterile, with a slight increase of protein but normal sugar and chlorides. The Wassermann reaction is normal, but the colloidal gold test may give a meningitic or even a parietic curve. The patients all recover, so that the condition is also called *benign lymphocytic meningitis*. The condition is now known to be due to a virus, as can be shown by inoculating monkeys with the cerebrospinal fluid. Incidentally this is about the only virus disease of the nervous system in which the virus can constantly be recovered from the cerebrospinal fluid. In the experimental animal the choroid plexus as well as the meninges are inflamed. The

distribution of lesions in man is not known, as the disease is not fatal. The virus seems to occur naturally in mice without producing disease, and it is possible that it may be transmitted from mice to man.

### VIRUS DISEASES OF THE NERVOUS SYSTEM

Certain filterable viruses have a special affinity for the central nervous system. They are neurotropic and cause some of the most serious diseases which afflict that system. There are some viruses which primarily attack the nervous system, *e. g.*, poliomyelitis, rabies, distemper of dogs, Borna disease of horses. Others do not ordinarily involve the nervous system, but when injected into the brain of an animal they produce serious or fatal results; examples are herpes febrilis, salivary gland disease of guinea-pigs, and vaccinia. There is still a third group of very common febrile diseases (measles, chickenpox, smallpox, vaccinia) in which injury of the nervous system occurs on rare occasions, usually during convalescence. Neurotropic viruses are peculiar in that they reach the central nervous system *via* peripheral nerves (cranial and spinal), traveling actually in the axis cylinder of the nerve fiber. Moreover they diffuse throughout the entire nervous system (central, peripheral and visceral), as bacteria spread throughout the vascular system in septicemia. Thus, when the virus of rabies is inoculated into the brain it can be recovered from the peripheral nerves some days later, although if a nerve is cut across, the distal part remains free from infection. That the virus travels by ways of the axons is demonstrated by the fact that when the virus of poliomyelitis is inoculated into the sciatic nerve of one leg it can be recovered from the opposite motor cortex, thus following the decussation of the motor path.

The three cardinal lesions of virus diseases of the central nervous system are inclusion bodies, cellular necrosis, and inflammation. Not all of these need be present, and unfortunately none of them is specific for viruses. It is very difficult to say how long a virus may remain in the nervous system once it has gained entrance. There may be more than fancy in von Economo's conception of the "encaged virus," which once having got in cannot get out again. It may do no harm until some accessory factor takes a hand, as in the case of herpes febrilis. Many of the viruses produce inclusion bodies in the affected nerve cells, *e. g.*, rabies, poliomyelitis, and Borna disease of horses. These and other fundamental matters have already been considered in the general discussion on viruses in Chapter VII.

Reference has already been made to the way in which neurotropic viruses travel along nerve fibers. This ability depends to some degree on the age of the individual. A neurotropic virus, which in young mice can travel from the nose to the olfactory region of the brain and thence to the thalamus and cortex causing fatal encephalitis, is held up in the olfactory region in older animals. This is probably due to the gradual development of a local immunity to the virus, and is of interest in relation to the prevention of such a disease as poliomyelitis.

Two great classes of lesions produced by neurotropic viruses may be distinguished. (1) Non-suppurative encephalitis or myelitis in which the infecting agent enters and *destroys certain groups of nerve cells*. Poliomyelitis, rabies, herpes, louping ill in the sheep, Borna disease in the horse (equine encephalomyelitis) are characteristic examples; epidemic encephalitis may be included with reserve, and possibly herpes zoster. (2) Encephalomyelitis in which the essential lesion is a *primary demyelination of nerve fibers*. The evidence that this group is caused by a virus is not absolute, only suggestive. An acute disseminated encephalomyelitis of this type may be primary, or it may follow the specific infectious fevers or vaccination. The demyelination, shown by the Weigert-Pal method, is striking and widespread. The question naturally suggests itself as to whether such demyelinating diseases as disseminated sclerosis and Schilder's disease should be included in this group. These latter diseases, however, are slowly progressive, whereas encephalomyelitis, if not fatal, ends in recovery. Our knowledge regarding the essential mechanism of demyelination and the question whether it is due to one or several classes of agent is still too rudimentary to justify us in concluding that it is due to a virus infection in every instance. In addition to the destructive and demyelinating lesions, both groups show perivascular collections of round cells. In Group I at least a proportion of these represent a true inflammatory reaction to the virus, all the more likely because polymorphonuclears are abundant in so typical an example as poliomyelitis. In Group II they are probably secondary to the myelin destruction, being proliferated microglial scavengers.

**Acute Anterior Poliomyelitis.**—Poliomyelitis or infantile paralysis is an acute infectious disease of the central nervous system which may appear in endemic or in epidemic form. It is a disease of young children, not of infants as the name would suggest, but in the large Winnipeg epidemic of 1928, 20 per cent of the cases were over fifteen years of age. An epidemic usually begins about the end of June and disappears with the first onset of cold weather. In spite of this clear-cut seasonal incidence which suggests an insect carrier, there seems to be little doubt that the disease is spread by personal contact. The carrier is not a patient, but a healthy person who harbors the virus in his nasopharynx or intestine. When a person develops the disease the virus in the throat at once loses its virulence, so that there is little danger of infection from the patient himself. More than one case seldom develops in a household. An epidemic of poliomyelitis is preceded by a carrier epidemic during which the virulence becomes raised. When this becomes sufficiently high, invasion of the nervous system occurs and a true epidemic begins, lasts a few months, and then rapidly disappears. During an epidemic the incidence of infection is much greater than the incidence of the disease.

**Pathogenesis.**—Poliomyelitis is caused by a filter-passing virus. The bacteriology has already been discussed in Chapter VII. The virus is strictly neurotropic. The disease can be reproduced in the monkey by

intracerebral inoculation of infected spinal cord. At least one human strain (Lansing strain) has been transferred through the monkey to the cotton rat and then to white mice (Armstrong). It is of interest to note that the virus is now non-pathogenic for the monkey and can be used for immunization. The monkey can be infected by painting the virus on the nasal mucosa. As no infection occurs when the olfactory nerves are cut, it is evident that infection passes along these nerves to the olfactory bulbs, which show marked inflammatory and degenerative lesions, and thence to the brain and spinal cord. These results have been applied to man, and it has long been presumed that the portal of entry was the nasopharynx and the olfactory tract. On the other hand it is now admitted that no lesions are found in the human olfactory bulbs, nor does blockage of the olfactory route by spraying the roof of the nasal passages with zinc sulphate offer any protection, although this procedure protects the monkey against infection from the nasopharynx. Yellow fever and rabies, both virus diseases, can be transmitted to the monkey by the nasal route, but no one suggests that this is the usual method of infection in man.

It is now known that the poliomyelitis virus can be isolated from the stools both in active and convalescent cases, sewage, the wall of the small and large intestines, and the mesenteric lymph nodes (Paul and Trask). It is indeed twice as easy to find the virus in stools as in nasal washings, especially in abortive cases, and the stools may remain infective for many weeks. These results suggest that poliomyelitis is primarily an intestinal rather than a respiratory tract disease. This would agree with the seasonal incidence. When the virus is administered orally to the monkey its passage from the intestine to the central nervous system can be traced.

From the standpoint of the human disease, however, the most important contribution is that of Faber and Silverberg, who traced the course of the virus in eight patients dying in the acute stage by studying the distribution of the lesions demonstrated histologically. In general the evidence of penetration through the upper alimentary and respiratory tracts was far more striking than through the lower alimentary tract. The pharynx, which is exposed to infection both from the nose and the mouth, was a specially favorable source for penetration of the virus. There was no single portal of entry, nor any support of the concept of an exclusive channel for all cases such as the olfactory and the intestinal. In no instance was the olfactory tract the route of infection. Invasion through the sympathetic results in initial involvement of the central nervous system at the spinal level; invasion through the other principal channels (the fifth, ninth and tenth cranial nerves) results in initial involvement at the level of the brain stem (midbrain, pons, medulla). This does not necessarily determine the site of initial paralysis.

The suggestion that poliomyelitis is primarily an intestinal rather than a respiratory tract infection has directed attention to the possibility of insect vectors. It was soon found that the virus could be

demonstrated in the bodies of green bottle and blow flies caught in epidemic areas and near the dwellings of poliomyelitis patients (Trask and Paul). On the basis of these experimental facts it has been suggested that human infection is mainly carried by flies. Clinical and epidemiological observations, however, do not support this view. It appears probable that the common method of infection is by passage of the virus from person to person by means of respiratory and oral transfer. Howe and his associates have shown that the virus can be obtained much more readily by means of oropharyngeal swabs than by the classical method of nasal irrigation. The virus was obtained in as high as 50 per cent of a small group of cases. This suggests the possibility of air-borne infection, at least in some cases in man. The history of the experimental work on poliomyelitis shows that the fact that a disease or lesion can be produced in a certain way in an experimental animal is no proof that it is produced in that way in man. The immunity which follows the disease is life-long, thus agreeing with the rule of virus diseases in general. A second attack is very rare. Immune bodies can be demonstrated in the blood of the patient during the remainder of his life.

**Symptoms.**—Although the disease is called infantile paralysis there may be no paralysis. These cases are spoken of as abortive forms; they remain in the preparalytic stage. Perhaps immunity develops in time to prevent the paralytic lesion. The child is feverish, irritable, with rigidity of the neck and a stiff back. The diagnosis in this stage, important as regards early immune serum treatment, depends on a healthy clinical suspicion and lumbar puncture. When paralysis develops, usually on the second or third day, it attains its maximum at once, and as a rule shows no subsequent extension. This again may be attributed to the rapid immunity. Only one arm or leg may be involved, or both legs (paraplegia). There may be bulbar symptoms with facial paralysis, squint, difficulty in swallowing, and respiratory failure. In the bulbar type there may be no spinal symptoms. In addition to motor weakness, pain is a constant symptom. This is usually pain on passive movement, but there may be spontaneous pain in a limb.

**Lesions.**—The lesions are always widely distributed throughout the central nervous system, although the symptoms (monoplegia, etc.) may suggest a very limited involvement. The lumbar enlargement of the cord is the most frequent site of lesions, followed by the cervical enlargement. The most marked lesions are in the anterior horn, but the posterior horn is also involved. Although the disease is called a myelitis, the brain is invariably involved in cases that come to autopsy. The severe cerebral lesions are confined to the brain stem (medulla, pons, and mid-brain), they are slight or absent in the basal ganglia, and practically never found in the cerebral cortex. In addition to the cord lesions there is involvement of the dentate nucleus of the cerebellum, the Gasserian ganglion, posterior root ganglia, and anterior and posterior nerve roots. It is evident that the virus has spread far and wide through the central nervous system. The lesions are both inflammatory and degenerative. The inflammatory lesions are the result, not the cause, of the degeneration. Sometimes, however, as in



the brain stem, inflammation may be much more evident than any demonstrable neuronal degeneration.

The cord is swollen on account of edema, and bulges when cut across. The gray matter may be hyperemic. The meninges are congested and may show slight inflammatory change, but this is seldom marked, thus agreeing with the absence of marked cellular changes in the cerebrospinal fluid. The so-called meningeal symptoms characteristic of the preparalytic stage are apparently not due to meningeal inflammation, as can be shown convincingly in the experimental animal.

The *inflammatory lesions* are best studied in the gray matter of the anterior horn of the spinal cord (anterior poliomyelitis) and in that of the pons and medulla, but the white matter does not escape. There is great congestion and hemorrhages are frequent. The vessels are surrounded by collars of inflammatory cells similar to the perivascular collars in epidemic encephalitis.

In addition to the perivascular lesions, diffuse and focal collections of inflammatory cells are present in the interstitial tissue. The focal collections may show necrosis. For the first few days the inflammatory cells are polymorphonuclears. These are then replaced by small round cells which have the appearance of lymphocytes, but when stained with silver they are seen to be microglia. Only the naked nuclei are stained in a hematoxylin and eosin preparation, but the silver brings out all the characteristic processes of the microglia cell. There is an enormous proliferation of microglia at an early stage of the disease; many of the cells lose their processes and become converted into neuronophages (see below). The astrocytes do not proliferate in the acute stage, but form the subsequent scar.



FIG. 442.—A large degenerated ganglion cell in poliomyelitis. The cell has lost its nucleus and its Nissl's granules.  $\times 600$ .

The *degenerative lesions* chiefly affect the motor cells of the anterior horn of the spinal cord, although the cells of the posterior horn Clarke's column and the posterior root ganglia may also suffer. Every degree of degeneration may be seen, from loss of Nissl's granules (chromatolysis) and eccentricity of the nucleus to complete disappearance of the cell. (Fig. 442.) Not a single ganglion cell may be seen in the section. The process of cell death and disintegration may be incredibly rapid,

as can be seen in the experimental animal. This agrees with the suddenness and completeness of the paralysis. The dead cells may be surrounded and invaded by phagocytes, a process known as neuronophagia. Most of the neuronophages are Hortega cells (microglia), but some polymorphonuclears may be seen. Degenerative changes are never marked in the brain, although the inflammatory lesions may be severe. Intranuclear inclusions are present in degenerating nerve cells in the early stage, but not when the cell has become necrotic (Hurst); the material must be fixed in sublimate-formol and stained with Giemsa or eosin-methylene blue.

The *end-result*, seen when the cord is examined long after the acute illness, is atrophy of the anterior horn on one or both sides. The nerve cells are replaced by astrocytes, and there is well-marked gliosis and fibrillar formation. The motor fibers arising from the destroyed cells disappear, as can be seen in sections stained with Weigert's myelin sheath stain. The paralyzed muscles show atrophy, fatty infiltration, and replacement by connective tissue.

**The Relation of Symptoms to Lesions.**—There is little or no opportunity for autopsy examination in the preparalytic stage, but observations on the experimental animal suggest that the so-called *meningeal irritation* (stiffness of the neck, irritability) is not due to inflammatory changes in the meninges, in spite of the fact that the cell count in the spinal fluid is highest at this stage. The initial "*systemic*" symptoms, such as fever, drowsiness, anxiety, heightened sensibility to pain, headache, and vomiting, may be explained by involvement of the thalamus and hypothalamus. The *pain* is probably due to lesions in the posterior root ganglia and in the posterior roots themselves. The *paralysis* is easily explained by the destruction of the motor cells in the anterior horn. Groups of motor cells may be picked out while neighboring groups are spared, and the lesions may be much more marked in the anterior horn on one side or may be confined to that side. This serves to explain the fact that the paralysis may be confined to one limb or even to one muscle or group of muscles. Facial nerve palsy and paralysis of other cranial nerves are due to lesions in the brain stem. Difficulty in swallowing with regurgitation of fluids through the nose (paralysis of the palate), respiratory failure (to which death is usually due), and other signs of bulbar paralysis are caused by lesions in the medulla.

**Cerebrospinal Fluid.**—The cerebrospinal fluid shows changes resembling those of epidemic encephalitis and tuberculous meningitis, but with certain differences. The fluid is clear or slightly opalescent, and occasionally a fine web may form, such as is seen in tuberculous meningitis but which never occurs in encephalitis. In the preparalytic stage the cells are high and the globulin low. As the disease progresses the cells fall and the globulin rises. In the Winnipeg epidemic of 1928, 80 per cent of the cases had a cell count between 10 and 200. The cells are mainly lymphocytes, but in the earlier stages there may be over 50 per cent polymorphonuclears. The sugar and chlorides are unchanged. In the Winnipeg cases a mid-zone reaction with the colloidal gold test was common.

**Theiler's Disease.**—In 1938 Theiler described a form of spontaneous encephalomyelitis in mice due to a virus. The disease is of interest because it bears a striking resemblance to human poliomyelitis (it has been called "poliomyelitis of mice"), and because the virus is found in the intestine of normal mice. An analogy may be drawn between these facts and the theory that poliomyelitis is primarily an intestinal infection.

**Encephalitis.**—Inflammation of the brain may be bacterial or viral. Bacteria cause a *suppurative encephalitis* in the form of small abscesses scattered throughout the brain, which may be microscopic or visible to the naked eye. This occurs in pyemia due to various pyogenic bacteria, and in bacterial endocarditis, where the lesions are often microscopic. Such conditions are terminal, and therefore not of great clinical interest.

*Virus encephalitis* constitutes a group of diseases, some of which are epidemic. In some the lesions represent a non-suppurative inflammation characterized by perivascular collections of macrophages, lymphocytes and plasma cells with accompanying degeneration of nerve cells. In others, particularly the postinfectious types, demyelination is the outstanding feature. The principal examples of virus encephalitis are: (1) type A encephalitis (von Economo), (2) type B encephalitis (St. Louis), (3) equine encephalomyelitis, and (4) acute disseminated encephalomyelitis.

**Type A Encephalitis.**—This is also known as epidemic encephalitis and encephalitis lethargica. Other forms of encephalitis may be epidemic and associated with lethargy, and as this type was first described by von Economo in Vienna in 1917, it is often known by his name. It appeared like a bolt from the blue in 1917, spread all over the world in pandemic form, returned more than once to a locality, and then vanished. Fresh cases are very seldom seen now. On general grounds it must be assumed that the disease is due to a virus, but this has never been proved.

**Symptoms.**—To attempt to give an adequate account of the symptomatology of epidemic encephalitis would be ludicrous in a textbook of pathology, for almost every known neurological symptom may be produced. Moreover the epidemic gradually changed its clinical manifestations. Winnipeg was visited by two epidemics, the first in the winter 1919–1920, the second at the beginning of 1923. In the *first epidemic* the patient was dull, lethargic, somnolent, and showed oculomotor disturbances. He would lie like a log in bed with drooping lids or closed eyes, the lines of expression all ironed out, sunk in a stupor which no external stimuli could penetrate, the flash and speed of the mind gone, the dim rushlight of reason hardly flickering. In the *second epidemic* the picture had changed completely. Body and mind were now keyed to full activity. The muscles were in a state of constant movement, which was paralleled by a condition of mental excitement. Words came in a torrent, rationally at first, but drifting away into delirium. Occupation formed the main topic of conversation: the teacher was continually teaching, the merchant was casting up accounts, the builder planning new houses. The first picture was akinetic, the second hyperkinetic. It must be noted, however, that more than one-half the 1923 cases developed lethargy and somnolence sooner or later.

In addition to fever and somnolence, oculomotor palsies are extremely common, causing diplopia, strabismus, and ptosis. The hyperkinesia manifests itself by every variety of choreiform and athetoid movement, as well as clonic spasm of various kinds. Rigidity, a "muscle-bound" condition, is present in the acute stage, but is far more pronounced in chronic encephalitis, giving the well-known condition of Parkinsonism or postencephalitic paralysis agitans, with its mask-like face, stoop, flexed arms and wrists, and mincing steps. Some 20 per cent of the cases developed some degree of Parkinsonism,

Other postencephalitic conditions which may be mentioned are narcolepsy and oculogyric crises (sudden attacks in which the eyes are fixed in a conjugate position). Among the most distressing of the sequelæ in children are profound emotional and moral disturbances, with disintegration of the mind and character.

**Lesions.**—The gross appearance of the brain is not characteristic. Microscopically the chief lesion is the familiar perivascular collars of chronic inflammatory cells. (Fig. 443.) In contrast to poliomyelitis there are no polymorphonuclears, no inflammatory foci, no areas of necrosis. Congestion is marked, and small hemorrhages are frequent. The lesions are most numerous in the periaqueductal region of the mid-brain, but they are also marked in the basal ganglia, pons and

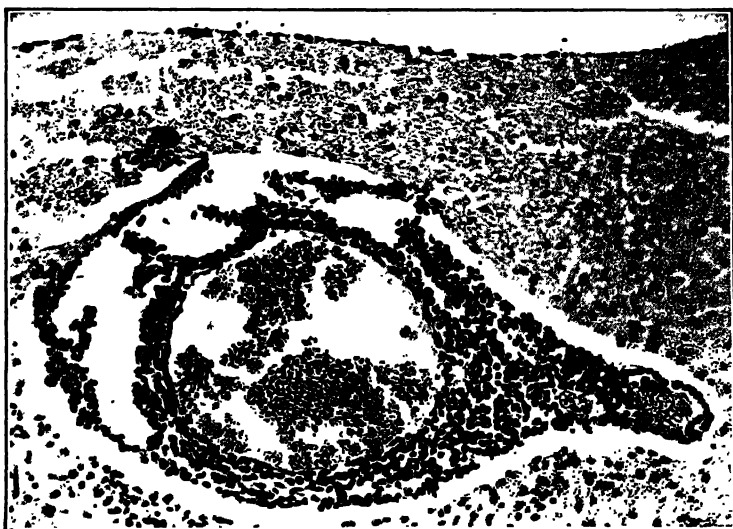


FIG. 443.—Epidemic encephalitis. Collar of cells around inflamed vessel in floor of fourth ventricle. The cells are in the true perivascular space.  $\times 200$ .

medulla. The cerebral and cerebellar cortex are not affected. Degeneration and disappearance of the pigmented cells of the substantia nigra in the mid-brain is a striking feature in the chronic stage, and there is also cellular degeneration in the globus pallidus. These structures are stations on the extrapyramidal tract, the primitive motor pathway, and the lesions serve to explain the motor helplessness and rigidity.

The *cerebrospinal fluid* shows no characteristic changes except that the sugar content tends to be high, due to an accompanying hyperglycemia.

**Type B Encephalitis.**—During the fall of 1933, an epidemic of encephalitis broke out in St. Louis and the surrounding district, which has been called encephalitis B. There was a recurrence in 1937. While resembling lethargic encephalitis, it appears to be more closely related to an epidemic reported

from Japan in 1924. Indeed, it is identical with the latter clinically and pathologically, although it reacts differently serologically. The disease differs from the lethargic forms in the following respects. Somnolence is uncommon, convulsions are frequent, there is a remarkable absence of the usual oculomotor palsies (ptosis, strabismus, diplopia), there are no sequelæ, the lesions are at higher levels (frequently in the cerebrum), there is no special localization in the mid-brain. Monkeys and mice are successfully infected by intracerebral inoculation of brain tissue and also by the intranasal route. The St. Louis convalescent serum protects these animals against the St. Louis virus, but not against the virus from the Japanese cases. The disease is probably transmitted by mosquitoes.

**Equine Encephalomyelitis.**—Horses suffer a fatal form of encephalomyelitis, a virus disease which appears in epidemic form. In 1938 there was a widespread epidemic of this disease in the United States and Canada. In a number of instances persons, particularly children, fell ill on farms where there were sick horses, and in fatal cases the same virus was found in the human patient and the horse. The human disease runs a very severe clinical course, with a fairly high cell count in the cerebrospinal fluid. In the late summer and during the autumn of 1941 over 1000 cases occurred in Manitoba and Saskatchewan due to so-called Western strain of virus, and 1080 cases in North Dakota. At autopsy the picture is that of an acute disseminated encephalomyelitis with intense congestion, perivascular collections of polymorphonuclears, and in places an acute arteritis. In addition there is neuronal degeneration and areas of actual necrosis. The lesions are widely distributed throughout the cortex, basal ganglia, pons, medulla, and cervical cord. The polymorphonuclear exudate is reflected in the cerebrospinal fluid, which shows a high cell count in which from 60 to 90 per cent of the cells may be polymorphonuclears.

The disease is readily transmissible to mice by intracerebral injection of brain tissue. Human infection is probably due to mosquitoes, but this has not been proved. Specific antibodies are found in the blood of domestic birds and mammals during an epidemic. Chickens and pigeons seem to serve as a reservoir of the infection. The virus can be transmitted to these birds not only by mosquitoes but also by ticks. The latter vector can pass on the virus to their offspring for innumerable generations. The evidence is conclusive that this is a virus disease; this is not true of the lethargic form of encephalitis.

There are two varieties of the disease, known as Eastern and Western. The Eastern form, prevalent in the Atlantic states, is the more virulent. Horses can be protected by a vaccine of virus grown on chick-embryo.

**Acute Disseminated Encephalomyelitis.**—The very occasional development of encephalitis as a result of one of the infective fevers has long been recognized. During recent years there has been a marked increase in the number of cases of acute and widespread involvement of the central nervous system either following some febrile disorder or occurring spontaneously. As these cases all have a similar if not common pathology, characterized by scattered patches of perivascular demyelination associated with an inflammatory reaction, they may

conveniently be considered under the heading of acute disseminated encephalomyelitis. Three main types may be distinguished: (1) post-vaccinal encephalitis, (2) encephalitis following infectious fevers, and (3) spontaneous encephalomyelitis.

*Postvaccinal encephalitis* has come into prominence since 1922, particularly in England and Holland. It is the most dangerous form of disseminated encephalomyelitis, with a mortality of from 25 to 50 per cent. The incidence in England is 1 in 50,000 vaccinations, while in Holland it is 1 in 5000. The onset, usually about the eleventh day after vaccination, is acute and the course rapid, with fever, vomiting, headache, squint, and sometimes upper motor neurone paralysis. It is possible that the vaccine virus is not directly responsible for the encephalitis, but may activate a virus lying dormant in the body. This is not so far-fetched as it sounds, for it is known that 80 per cent of normal guinea-pigs harbor a virus in the salivary glands, which when injected into the brain produces a fatal encephalitis (Cole and Küttner).

*Encephalitis following fevers* is most often a sequel to *measles*. More rarely it follows other virus diseases such as mumps, chicken-pox, and whooping cough. Post-measles encephalomyelitis may be more of a myelitis than an encephalitis. The characteristic symptoms are paraplegia, first flaccid and later spastic, incomplete or dissociated anesthesia, and loss of sphincter control. Fortunately these symptoms are usually only temporary.

*Spontaneous encephalomyelitis* is another disease of the central nervous system which has become considerably more common in recent years. It is often mistaken for epidemic encephalitis, but the prognosis is very much better, for recovery is the rule and serious sequelæ are quite uncommon. In adults the clinical picture suggests a myelitis, while in children it is more a meningoencephalitis. In the cerebral form there are symptoms of meningeal irritation, convulsions, or hemiplegia. Even with marked meningeal symptoms the cerebrospinal fluid is often normal, but the cell count may be increased. The spinal symptoms are pain and paresthesias in the legs, weakness and even temporary paralysis of the legs, with loss of the deep reflexes but a positive Babinski sign. Nystagmus is common, but diplopia, so characteristic of epidemic encephalitis, is very rare and the cranial nerves usually escape.

**Lesions.**—In all forms of acute disseminated encephalomyelitis the essential lesion is perivascular demyelination. (Fig. 444.) The lesions are scattered in patchy form through the gray and white matter of the brain and cord. They are most marked in the pons, medulla, and the lumbar region of the cord, in contrast to the lesions of epidemic encephalitis which are most numerous in the mid-brain. The demyelination is best seen when the tissue is stained with iron hematoxylin or Weigert's myelin stain, the lesions standing out as pale patches on a black background. These lesions are very similar to those of disseminated sclerosis, but the removal of the myelin is extraordinarily rapid. Perivascular inflammatory cells are also present and these cells

may form a broad zone outside the adventitia extending for some distance into the brain substance, quite unlike the compact collars of cells seen in epidemic encephalitis. The pale areas may contain many scavenger cells (compound granular corpuscles) derived from the microglia.

**Wernicke's Disease.**—This rare condition, known also as *acute superior hemorrhagic polioencephalitis*, is marked clinically by paralysis of the eye muscles, stupor or excitement, and usually death within a few days. The lesions are curiously restricted. The corpora mammillaria are constantly affected; in addition there may be lesions in the hypothalamus, thalamus, and periaqueductal gray matter. The gross lesions are congestion and hemorrhage. Microscopically there is chromatolysis of ganglion cells, hemorrhage, and glial proliferation, but no true inflammation. The condition presents a clear cut pathological entity, but one which is easily overlooked at autopsy unless borne in mind. The hemorrhagic lesions in the walls of the third ventricle and aqueduct and the floor of the fourth ventricle are well brought out by Pickworth's benzidine stain, as is beautifully shown in Campbell and Biggart's paper. When Wernicke originally described the condition in 1881 he ascribed it to alcoholism, but it is now believed to be a deficiency disease, because similar lesions can be produced experimentally by vitamin B<sub>1</sub> deficiency.

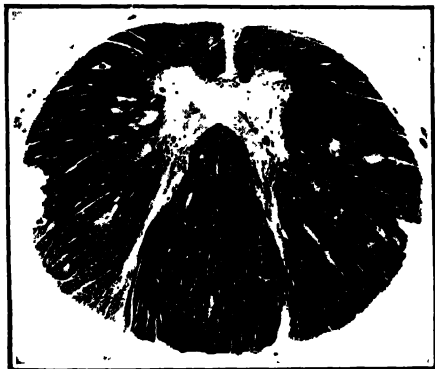


FIG. 444. Post-vaccinal encephalomyelitis; myelin sheath stain.  $\times 7$ .

**Lead Encephalitis.**—In the chronic lead poisoning of children (see Chapter XIII), one of the most dreaded complications is lead encephalitis. This differs from other varieties of encephalitis in that it takes the form of an extreme cerebral edema caused by the presence of lead in the brain. A similar condition can be produced experimentally in animals by the continued administration of small quantities of lead. The brain is remarkably swollen, the cerebral convolutions are flattened, the ventricles are compressed, and the medulla is pressed down into the spinal canal. The cerebrospinal fluid pressure may be 700 mm. of water as compared with the normal pressure of 120 mm.

**Rabies.**—Rabies or hydrophobia is an acute inflammatory disease of the nervous system, which is transmitted to man by the bite of a rabid animal, usually a dog, sometimes a wolf. It is caused by a filter-passing virus, and it has already been considered in connection with virus diseases in Chapter VII. In this place it is sufficient to recall that the virus passes along the axis cylinders of the nerves to reach the central nervous system, in this respect resembling the virus of poliomyelitis and herpes simplex. The characteristic cytoplasmic inclusion bodies (Negri bodies) are found in the nerve cells of the *hippocampus major*, medulla and cerebellum.

**Herpes.**—Like rabies, poliomyelitis, and probably epidemic encephalitis, herpes is a disease caused by one of the filter-passing viruses. It is characterized by the formation of small vesicles. There are two

distinct forms: (1) herpes zoster or shingles in which the vesicles follow the distribution of a sensory nerve, and (2) herpes simplex in which there is no such distribution. An attack of the former is followed by lasting immunity, but in the case of the latter there is no immunity. They are caused by entirely different viruses.

**Herpes Zoster.**—This is an inflammatory condition of the posterior root ganglia or the Gasserian ganglion. It is the sensory analogue of poliomyelitis; the type of lesions in the nervous system and the condition of the cerebrospinal fluid is the same in the two diseases. Usually only one ganglion is involved, most often in the dorsal region. The eruption is always unilateral, running in a zone (zoster) as far as the middle line, and is preceded by neuralgic pains, which in old people may be very persistent and severe. The vesicles begin as papules, and may leave some scarring. The lesions in the ganglia are similar to those in the anterior horn in poliomyelitis, *i. e.*, congestion, hemorrhage, perivascular collections of lymphocytes, and degeneration of ganglion cells with neuronophagia. There is Wallerian degeneration of the nerve fibers in the posterior roots, in the peripheral nerves, and in the posterior columns.

**Herpes Simplex.**—This is the common form of herpes which may complicate pneumonia and other fevers (herpes febrilis). It usually occurs on the lips (herpes labialis), but may be on the cornea or external genitals. It differs from herpes zoster in being recurrent, not following the line of nerves, and causing no change in the cerebrospinal fluid. When the virus of herpes simplex is inoculated into the cornea of a rabbit it sets up a fatal encephalitis. In whichever part of the body the virus is inoculated, it passes along the axis cylinders until it reaches the central nervous system, where its presence can be detected by the appearance of the Lipschutz bodies which have already been described in Chapter VII. These bodies are found in the epithelial cells at the site of inoculation (skin, cornea), as well as in the nerve cells. The lesion in man is inflammation of a sensory nerve ganglion.

**Louping Ill.**—Although this is a virus disease of sheep, it may be considered here because of the interest of its lesions. As the Scotch name indicates, it is characterized by progressive incoördination and cerebellar ataxia. The disease can be reproduced both in the mouse and monkey. In the monkey there is a diffuse encephalomyelitis, but the principal lesion is a massive destruction and astonishing disappearance of the Purkinje cells of the cerebellum. The virus has the same strange selective action on these cells as the virus of poliomyelitis has on the motor cells of the anterior horn of the spinal cord. Laboratory workers in contact with the virus are said to have developed mild infections.

**Myelitis.**—Acute inflammation of the spinal cord is rather rare. It may be *traumatic*, due to injury of the spine, or *infective*, due to septic embolism, to the infective fevers, or to syphilis. The *syphilitic* form is discussed in connection with syphilis of the nervous system. There is usually complete paralysis below the site of the lesion. This is usually in the lumbar region, so that the legs show a flaccid lower motor neurone paralysis with loss of deep reflexes and loss of sphincter control. There



may be anesthesia below the lesion and hyperesthesia at the level of the lesion. If the lesion is in the cervical region both arms and legs will be paralyzed, but while the arms show a lower motor neurone paralysis, the legs develop an upper motor neurone type of paralysis, as the lower neurones remain intact.

**Lesions.**—The inflammation is usually confined to one or at the most a few segments of the cord; this is called *transverse myelitis*, because the entire thickness of the cord is involved. Occasionally the inflammation may be diffused throughout the cord; this is *disseminated myelitis*. The affected part is soft and flattened, the distinction between gray and white matter is lost, and liquefaction may occur. *Microscopically* there is great destruction of nerve cells and nerve fibers, of gray and white matter. Among the débris are large numbers of scavenger cells derived from the microglia. Perivascular collections of inflammatory cells are present in the surrounding tissue. The degeneration of the nerve fibers can be demonstrated in early cases by Marchi's method and in old cases by the Weigert myelin sheath stain.

**Landry's Paralysis.**—This very rare disease is an acute ascending paralysis, in which first the legs, then the arms, and finally the intercostal muscles and diaphragm are paralyzed, with death from respiratory failure. Sometimes the paralysis is descending instead of ascending. The pathological changes are remarkably slight, for death usually occurs in three or four days. There is degeneration of the motor cells of the spinal cord and breaking up of the medullary sheaths of the corresponding nerve fibers. There are no perivascular collars of cells. The mode of progression suggests a virus disease.

## SYPHILIS OF THE NERVOUS SYSTEM

Syphilitic *infection* of the nervous system is frequent and early. The cerebrospinal fluid, that delicate mirror in which are reflected so many of the pathological changes which occur in the brain and spinal cord, shows that infection is common in the second stage and may even occur in the primary stage. But to say that syphilitic *disease* of the nervous system is common is quite another matter. The production of a tissue immunity seems to protect the nervous tissues. It has been suggested that syphilis of the nervous system is due to a particular neurotropic strain of spirochete, in contrast to the ordinary strains which are epitheliotropic. The fact that a number of men infected from the same woman have developed brain lesions tends to support this idea, but the foundation on which it is based cannot be regarded as firm.

The disease may take a number of forms, which may be divided into lesions of the *interstitial* and the *parenchymatous* tissues. The first is called neurosyphilis or cerebrospinal syphilis. It affects the meninges, the bloodvessels, and the perivascular extensions of the meninges, and may be divided into a localized form, the gumma, and a diffuse form known as meningoencephalitis or meningomyelitis. The parenchymatous structures (the neurones) may be affected chiefly in the brain, giving general paresis, or in the cord giving tabes dorsalis. These four types will be considered separately.

1. **Gumma.**—A gumma of the brain is not common at the present day, and it is much less common in the cord. As it is a lesion of the meninges it occurs at the surface, usually over the vertex. When it is situated in the substance of the brain it arises from the perivascular extensions of the pia-arachnoid. It is firm, gray in color, and may become as large as a tangerine orange. It produces the symptoms of an intracranial tumor. The microscopic picture is the usual syphilitic one, *i. e.*, a central area of necrosis surrounded by lymphocytes, plasma cells, and macrophages.

2. **Syphilitic Meningoencephalitis.**—Here there is a diffuse lesion of the meninges, but the superficial layers of the brain are also involved to a varying degree. The meningeal exudate is usually most marked at the base of the brain, forming a milky exudate in the interpeduncular space, or the whole hemisphere or cord may be covered by a thick sheath. The cranial nerves in the region of the interpeduncular space are often involved, particularly the third, fourth, and sixth, so that ptosis, strabismus, and diplopia are common. These symptoms are often characteristically fleeting. There may be optic neuritis and dimness of vision. *Microscopically* the cells of the exudate are lymphocytes with a few plasma cells, and it may be impossible to be sure that the condition is syphilitic unless areas of gummatous formation are present. The perivascular sheaths are also filled with a similar exudate, and it is these which constitute the encephalitis. *Syphilitic myelitis* is a much more distinct entity than syphilitic encephalitis, and is indeed the commonest form of myelitis. It is of the transverse type, limited to a few segments. Thrombosis of the diseased vessels is probably a major etiological factor, as a result of which there is softening of the cord and marked destruction of nerve cells and fibers. *Syphilitic arteritis* is a marked feature of all the lesions. The adventitia is infiltrated with round cells and the intima is uniformly thickened. The result of this endarteritis obliterans is to produce great narrowing or actual closure of the lumen, which leads naturally to thrombosis. Aneurism formation is not a result of cerebral syphilis, for the diffuse thickening does not weaken the vessel as do the patchy lesions of syphilitic aortitis. There may be a gummatous process around the vessel, a gummatous arteritis.

**Cerebrospinal Fluid.**—In acute syphilitic meningitis the reaction is severe and there is often a lymphocytosis of 500 or more. This high cell count is very suggestive of syphilitic meningitis. The protein content is high, the Wassermann reaction is positive, and the colloidal gold curve may be of the parietic or mid-zone types. A gumma causes much slighter changes, the Wassermann and colloidal gold reactions are weak or negative, and the lymphocytosis and protein increase are slight. If the lesions are chiefly vascular, the fluid may be practically normal.

3. **Tabes Dorsalis.**—Tabes dorsalis or locomotor ataxia is a syphilitic disease of the cord, a late manifestation usually coming on from ten to fifteen years after the primary infection, although the interval may occasionally be as short as two years. The indirect evidence that the

disease is syphilitic is conclusive, but spirochetes have very seldom indeed been found in the cord, nerve roots or ganglia, and the lesions bear no resemblance to the ordinary changes produced by syphilis.

**Symptoms.**—The symptoms may be divided into the following groups: (1) sensory disorders, (2) disorders of coördination, (3) disorders of the reflexes, (4) disorders of the cranial nerves, (5) visceral crises, and (6) trophic disorders. These will be considered in detail in discussing the relation of the lesions to the symptoms, but it may be said in outline that the chief features are severe pains in the legs, paresthesias, loss of muscle sense, loss of the power of muscular coördination, loss of the deep reflexes and the reaction of the pupil to light, optic atrophy, attacks of abdominal pain and vomiting, and painless destructive lesions of the skin and joints.

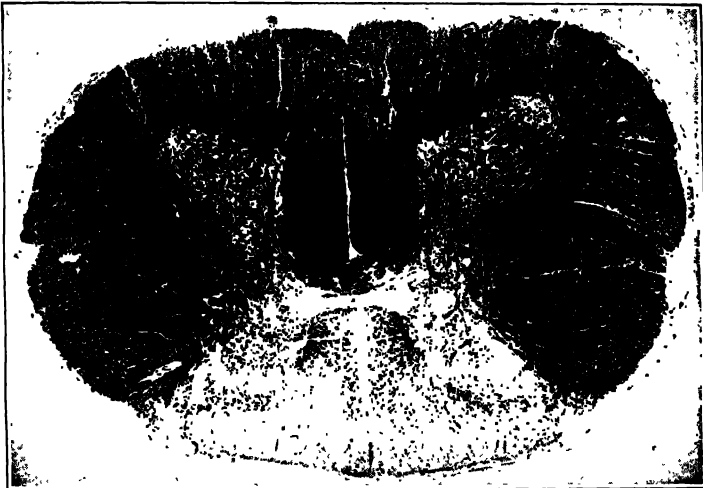


FIG. 445.—*Tabes dorsalis*: degeneration of posterior columns. (Weigert's myelin sheath stain.)

**Lesions.**—As already stated, the essential lesion in *tabes* is not a characteristic syphilitic one, although in early cases (which are seldom seen at autopsy) there is said to be syphilitic inflammation of the meninges. The true tabetic lesion is a degeneration and disappearance of the posterior columns of the cord and their replacement by neuroglial tissue. This lesion can be recognized with the naked eye. The pia over the dorsal columns is thickened and adherent. The surface of these columns is no longer convex, but flattened or concave, and on the cut surface they are gray and translucent so that they stand out clearly from the rest of the white matter. It is the wasting of the dorsal columns which gives the disease its name (*tabes*, wasting). The posterior nerve roots are atrophied and shrivelled in comparison with the plump anterior roots, but this distinction is not so easy to recognize.

The *microscopic change* is seen in sections stained with Weigert's myelin sheath stain or the simpler iron hematoxylin. The normal

white matter is stained black, but the degenerated posterior columns remain unstained. (Fig. 445.) The lesions are usually most marked in the lumbar region, but in the so-called cervical tabes they are confined to the cervical region. The first change is a demyelination, and droplets of myelin can be demonstrated by the Marchi method or Scharlach R. The axis cylinders become disintegrated, and in time the whole of the medullary sheath disappears. There is proliferation of astrocytes and a replacement gliosis. It is only the exogenous fibers of the posterior columns which degenerate, *i. e.*, those which enter the cord in the posterior nerve roots and whose cells of origin are in the posterior root ganglia. The short endogenous fibers, which arise from cells in the cord and pass up or down for two or three segments, remain unaffected. The long fibers pass up the cord to end in the nucleus gracilis and nucleus cuneatus in the medulla, and those which enter in the lumbar region are continually displaced to the middle line by fibers entering higher up. It follows that if the disease is confined to the lumbar afferent fibers, only the column of Goll in the cervical region will be degenerated, whereas if all the afferent fibers are affected there will be lesions of the column of Burdach as well.

Certain lesions are found *outside the cord*. The posterior nerve roots show the same degeneration and atrophy as do the dorsal columns. Degenerative changes have been described in the cells of the posterior root ganglia, but these are inconstant and must be regarded as secondary. When optic atrophy is present the fibers of the optic nerve are found to be degenerated.

The *pathogenesis* of tabes is a question of singular difficulty. Countless theories have sprung up, only to be cut down like grass as the result of further investigation. A primary syphilitic lesion of the posterior root ganglia with secondary degeneration of the afferent fibers would explain everything, but there is no such lesion. The popular theory at present is that of Richter to the effect that the spirochetes invade the posterior nerve roots and there cause the formation of a specific granulation tissue which slowly strangles the nerve fibers. Unfortunately for this theory it has been shown by Ruby Stern that this so-called granulation tissue is merely collections of arachnoid cells, and that they are found in many conditions other than tabes. She suggests that the syphilitic focus responsible for tabes may lie outside the central nervous system, possibly in the adventitia of the aorta, and that the syphilitic toxin passes along the afferent nerves (in the perineural lymphatics or the axis cylinders), leading to degeneration of the ascending fibers in the cord. Many years ago Orr and Rows showed that when celloidin capsules containing bacteria were placed in contact with afferent nerves, the toxins passed along the perineural lymphatics to the cord where they produced degeneration of the posterior columns indistinguishable from that of tabes dorsalis.

**The Relation of Symptoms to Lesions.**—*Sensory disturbances* include paresthesias, pain, and loss of muscle and vibration sense. The patient feels as if he were walking on something soft like cotton wool. "Lightning pains" of extreme severity shoot down the legs. The first effect of the lesion seems to be to set up violent impulses in the pain sensibility fibers and in the posterior nerve roots. There is also objective disturbance of pain sensibility in the shape of *analgesia* of the back and legs, so that the pain of lumbar puncture is not felt. The pain fibers end at once in the posterior horn of gray matter,

and the second relay of fibers does not pass up in the posterior columns, from which it is evident that the interference must be in the posterior roots, not in the spinal cord. There is loss of muscle sense or sense of position, so that when the eyes are shut the position of the foot is unknown, and the patient sways when standing (Rombergism). The vibration sense is lost, so that he cannot feel the vibration of a tuning-fork placed on the shin. As both muscle sense and vibration sense impulses pass up in the posterior columns, it is natural that they should be lost.

*Incoördination* is due to interference with the muscle sense. As the patient is not sure of the position of his feet, he walks unsteadily and with a wide base (locomotor ataxia), lifting his feet high and throwing them down forcibly (stamping gait). *Loss of deep reflexes* in the legs is due to interference with the short fibers which anastomose directly around the cells of the anterior horn. The reflex arc is thus broken and the deep reflexes lost. The knee-jerk depends on the integrity of the third and fourth lumbar segments, and the Achilles jerk on the fifth lumbar and first sacral. In very low lesions the knee-jerk is preserved but the Achilles jerk is lost. The *light reflex* in the pupil is commonly lost, though contraction on accommodation is retained (Argyll-Robertson pupil). The nerve center for the pupillary reflex is the oculomotor nucleus in the mid-brain, but the lesion is in the subependymal region of the aqueduct of Sylvius. In *optic atrophy* the optic nerve shows the same kind of lesion as the posterior nerve roots, but the way in which the lesion is produced is uncertain. The *visceral crises* are severe paroxysms of pain referred to various viscera (gastric, laryngeal, etc.). The cause is not known. The *trophic disturbances* are the most difficult to explain. The best known are Charcot's joint (a painless disorganization of one of the large joints), and the painless perforating ulcer of the foot. Possibly the analgesia which allows the parts to be severely traumatized may be more responsible than any loss of trophic nerve impulses.

**Cerebrospinal Fluid.**—There is a lymphocytosis of from 10 to 50. In tabetic crises, possibly attended by meningeal irritation, there may be hundreds of cells with many polymorphonuclears. The protein is slightly increased. The colloidal gold curve is of the luetic type. The Wassermann reaction is positive in about 70 per cent of cases. In an old case of many years' duration the fluid may be practically normal.

**4. General Paresis.**—This disease, also known as general paralysis of the insane and dementia paralytica, is the most fearful of all the results of syphilitic infection, although with modern treatment the prognosis is not nearly so hopeless as it used to be. The lesions are the direct result of the action of the spirochetes, for the latter can be demonstrated in the cerebral cortex. Other accessory factors are needed as well as infection with lues, although what these are we can only vaguely indicate by such phrases as "civilization and syphilization," "excess in *venere et baccho*," etc. Those who lead a restless, agitated, and dissolute life are in danger. The symptoms appear from ten to fifteen years after the primary infection. Similarly the juvenile form due to congenital syphilis appears about the age of ten years.

**Symptoms.**—The name dementia paralytica describes the disease fairly well, because there is a general motor weakness, and if left to itself the condition progresses remorselessly to complete dementia. The mental disorder first affects the faculties of judgment, reason, self-control, and there is an accompanying loss of moral sense. As Oppenheim says, the work of deterioration begins first in the higher life of the mind and soul. As the dementia increases, the mental structure crumbles to the ground. Delusions of grandeur lead

to a remarkable euphoria which contrasts strangely with the sad reality. The last stage is one of complete dementia. Tremors of the face, lips, and tongue are common. The speech is thick and characteristically slurring. The pupillary reflex is of the Argyll-Robertson type, with loss of reaction to light, but not to accommodation. Peculiar epileptiform or apoplectiform seizures ("paralytic seizures") may occur in which loss of consciousness may be followed by transient monoplegia or hemiplegia. Weakness of the muscles (paresis) is a constant feature of the disease, but never absolute paralysis.

**Lesions.**—The skull cap is thick, and there may be subdural hemorrhage with the formation of a thick membrane (pachymeningitis hæmorrhagica). The brain is small, with marked atrophy in the



FIG. 446.—Perivascular cuffing in general paresis.  $\times 85$ .

fronto-parietal region. The convolutions are wasted, the sulci widened, and there is a great compensatory excess of cerebrospinal fluid. The pia is thickened and adherent over the frontal lobe, so that when it is stripped off there is tearing or "decortication" of the surface. The lateral ventricles show a compensatory dilatation. The floor of the fourth ventricle is finely granular, giving it a frosted appearance, and the lateral ventricles may show the same condition to a lesser degree.

The *microscopic picture* is a mixture of syphilitic inflammation and tissue downfall. The meninges are densely infiltrated with lymphocytes and plasma cells. (1) The *inflammatory lesions*, which are most marked in the cerebral

cortex and the floor of the fourth ventricle, consist of dense perivascular collections of lymphocytes and plasma cells, the latter being especially numerous and characteristic. (Fig. 446.) These lesions are found throughout the entire thickness of the cortex. There may also be a diffuse infiltration of inflammatory cells. These lesions are to be attributed to the irritation produced by the spirochetes.

(2) The *degenerative lesions* are quite as marked, but they are more difficult to recognize unless one happens to be an expert neuropathologist. The general architecture of the cortex is completely lost, and the different layers can no longer be made out. There is a great outfall of cells, especially in the frontal and parietal regions. Most of the pyramidal cells may have disappeared. Those which remain show every degree of degeneration. The mechanism of this destruction is not at all obvious, for there is none of the gummatous destruction of the ordinary syphilitic process. The tangential association fibers suffer

greatly, as can be seen in Weigert preparations, and the pyramidal projection fibers also suffer owing to destruction of the large motor cells.



FIG. 447.—Granular floor of fourth ventricle in general paresis. The ependyma is desquamated from the mounds of neuroglia.  $\times 175$ .

(3) *Neuroglial proliferation* is marked, especially in the superficial layer of the cortex and in the walls and floor of the ventricles. The astrocytes multiply and form a dense feltwork of fibers. These are responsible for the pial adhesions and the decortication. In the floor of the fourth ventricle the glial proliferation causes an irregular heaping up of the floor. (Fig. 447.) This is the cause of the granularity already described. The granulations are covered by ependyma, but some of the summits may be bare. The microglia also proliferates, giving rise to large numbers of "rod cells (Fig. 448)," which form an intermediary stage between the microglia cell and the compound granular corpuscle. In sections of cerebral and cerebellar cortex and of basal ganglia the Prussian blue reaction shows iron-containing pigment in the cytoplasm of these cells and in perivascular spaces. The combination of the proliferation of "rod cells" and the presence of iron pigment in their cytoplasm is considered by Stern to be pathognomonic of general paresis.



FIG. 448.—Rod cells.  $\times 300$ .

The *spinal cord* may show degenerative changes in the pyramidal tracts owing to destruction of the motor cortex. There is sometimes a combination of tabes and paresis (*taboparesis*), with degeneration of the posterior columns. The pathogenesis of the two conditions, as we have already seen, is probably entirely different. The inflammatory lesions so characteristic of paresis are as notably absent in tabes.

**The Relation of Symptoms to Lesions.**—The clinical features are so varied and the pathological lesions so complex that little can be hoped from an attempt to harmonize them. The mental deterioration is probably connected with the disappearance of the tangential association fibers, and the disintegration of the frontal cortex is the basis of the final disintegration of the mind. The muscular weakness is due to degeneration of the motor nerve cells, and probably the tremors have a similar origin. The lesion causing the Argyll-Robertson pupil lies in the subependymal region of the aqueduct of Sylvius. The lesions responsible for the speech disturbance and the paralytic seizures are not known.

**Cerebrospinal Fluid.**—The changes are more marked and constant than in tabes, but in the late stage of dementia they become much less striking. The cells number from 30 to 100, and polymorphonuclears are often present, especially during convulsive seizures. Plasma cells are highly characteristic, but can only be seen in celloidin sections made of the centrifuged coagulum. The protein is increased. The Wassermann reaction is positive and intense in from 96 to 100 per cent of untreated cases. It may be positive in the fluid but negative in the blood, but only in late cases. The colloidal gold reaction gives a parietic curve.

### DISSEMINATED SCLEROSIS

This condition, also known as multiple sclerosis, is a chronic disease of the nervous system, characterized by curious remissions and relapses, and by the presence of multiple patches of sclerosis scattered diffusely throughout the gray and white matter of the brain and spinal cord. The incidence varies greatly in different countries. It is commonest in Switzerland, quite common in England, France, and Germany, fairly common in Canada and the United States, rare in South America, and unknown in China and Japan. The *cause* is unknown, but is almost certainly an infection. The lesions are very similar to, indeed identical with, those of acute infectious encephalomyelitis, especially postvaccinal encephalitis, and it is more than possible that disseminated sclerosis is also caused by a filter-passing virus. Spirochetes and other organisms have been described as the cause, but in none of these is there any real proof. The evidence of the lesions suggests a toxin acting on the tissues immediately around the bloodvessels.

**Symptoms.**—The patient, usually between the age of fifteen and thirty-five years, suffers from a great variety of sensory and motor disturbances, many of which are curiously and characteristically fleeting. There are paresthesias of various kinds in the hands and feet, spastic paralysis of the upper motor neurone type with exaggerated deep reflexes and a positive Babinski sign, loss of the abdominal reflex, and transient disturbance of the organic reflexes. The well-known *Charcot triad* of nystagmus, intention tremor, and staccato speech are late manifestations of incoördination. The cranial nerves may be affected, causing sudden blindness, pallor of the temporal side of each optic disc, and oculomotor palsies. The patient is absurdly cheerful, considering



the progressive and incurable nature of his ailment. Although progressive, the most remarkable remissions often occur, during which most of the symptoms may disappear.

**Lesions.**—The lesions are scattered widely through the white matter of the brain and cord, and can be seen and felt in the fresh specimen as well-defined gray translucent patches. The lesions are very numerous in the brain, being especially well marked in the pons, medulla, and cerebellar peduncles. There are patches in the optic nerve and optic chiasma. In the cord the lesions are most marked in the lateral columns (pyramidal tracts), but they are also present in the posterior columns.



FIG. 449. --Multiple sclerosis. There are irregular asymmetrical patches of degeneration in the posterior and lateral columns. (Weigert's myelin stain.)  $\times 8$ .

The *microscopic picture* varies with the stage of the disease. Disseminated sclerosis is an inflammation with subsequent demyelination and gliosis. If the autopsy is done during the *early stage*, which is seldom possible, the medullary sheaths are found to be breaking up into droplets of myelin which can be stained with fat stains (osmic acid, Scharlach R), and the vessels are surrounded by collars of cells. Some of these cells are true inflammatory cells (lymphocytes and plasma cells), but others are compound granular corpuscles filled with droplets of myelin. It would appear, therefore, that the condition is inflammatory in nature, with demyelination as the chief result. The lesions are very similar to those of postvaccinal encephalitis, but in disseminated sclerosis the production of the lesions is a much more gradual process. In the *advanced stage*, the stage usually seen at autopsy, there are multiple neuroglial scars surrounding the blood-vessels, chiefly in the white matter and to a lesser extent in the gray matter. In Weigert-Pal sections the scarred areas appear white on

a black background. (Fig. 449.) In these patches of sclerosis the axis cylinders may be wonderfully intact, thus accounting for the remarkable remissions of symptoms which may take place. Some of the axis cylinders degenerate and others disappear entirely. The astrocytes proliferate and the nerve fibers are replaced by a dense glial network. There is a remarkable absence of secondary degeneration above and below the lesions, so that the patches of degeneration remain isolated. In this respect the disease differs entirely from tabes which is a system degeneration, *i. e.*, a condition affecting an entire system of fibers. Evidence of inflammation such as perivascular collars of cells is entirely lacking in the late stages of the disease.

**The Relation of Symptoms to Lesions.**—The lesions are much more widespread than the severity of the symptoms would suggest. "Sclerosis creates multa, but not multum," as Oppenheim puts it. The comparative integrity of the axis cylinders explains the unexpected way in which such serious symptoms as paralysis or loss of vision may suddenly clear up. Lesions in the pyramidal tracts at different levels are responsible for the spastic paraplegia, exaggerated deep reflexes, and positive Babinski sign. The sensory changes are due to the lesions in the posterior columns. The absence of muscular atrophy and reaction of degeneration is to be expected from the fact that the anterior horns escape serious injury. The cerebellar incoördination, evidenced by nystagmus, intention tremor and scanning speech, is caused by lesions in the cerebellar peduncles which cut off the coördinating influences which play on the motor centers in the mid-brain and pons. The temporary loss of vision and the pallor of the temporal side of the discs are due to lesions of the optic chiasma or optic nerve. Diplopia, strabismus, and ptosis are caused by patches of sclerosis in the mid-brain.

**Cerebrospinal Fluid.**—With one exception this shows little change. There is a mild lymphocytosis in the early cases and a slight increase of protein, but in the advanced sclerotic stage these changes are absent. The exception is the colloidal gold reaction, which in about one-half the cases gives a paretic curve, though the Wassermann reaction is always normal.

**Encephalitis Periaxialis Diffusa. Schilder's Disease.**—This rare condition, which affects children and young adults, closely resembles disseminated sclerosis in its pathology, but it involves the cerebral hemispheres, not the brain stem and spinal cord. The disease is essentially a demyelination of the white matter of both hemispheres, the gray matter escaping untouched. The affected areas are soft and gelatinous, gray and translucent. The process usually starts in the occipital lobes and spreads forward, but it may begin in any part of the cerebrum. The *microscopic features* are similar to those of early disseminated sclerosis and postvaccinal encephalitis, *i. e.*, demyelination with destruction of the axis cylinders, perivascular collars of scavenger cells, and early gliosis. There is marked secondary degeneration of the affected paths. The cause of the condition is unknown.

The onset is acute and the course rapidly progressive but some cases may recover. The symptoms correspond with the lesions to a degree never seen in disseminated sclerosis. There is early blindness of cerebral type (occipital lobe), deafness (temporal lobe), sensory disturbances and loss of sense of position (parietal lobe), spastic paralysis (motor area), and mental deterioration (frontal lobe). Convulsions are common. The combination in a child of progressive blindness, progressive spastic paralysis, and progressive mental failure is pathognomonic.

Resembling this condition is "*Swayback*," a congenital demyelinating disease of lambs, characterized by incoördination of movement, tremors of the head, blindness, and spastic paralysis. There may be demyelination of an entire cerebral hemisphere. In some flocks as many as 90 per cent of the lambs born are affected.

## CHRONIC MOTOR NEURONE DEGENERATION

Three different clinical entities, all of them rare, may be grouped under this heading, for in all of them the underlying basis is a primary degeneration of the motor neurones, upper or lower or both. In *progressive muscular atrophy* the lesion is in the anterior horn, in *bulbar palsy* it is in the bulbar centers, and in *amyotrophic lateral sclerosis* both the upper and lower motor neurones degenerate. There is no involvement of the sensory side. The cause of the condition is unknown and its nature uncertain. It occurs in persons over middle age, there is nothing inflammatory about it, and it seems to be a pure degeneration, a gradual neuronal decay, an abiotrophy. It is possible that a food deficiency, vitamin or otherwise, may be responsible. In all three forms there is progressive muscular weakness with atrophy and fibrillary tremors in the affected muscles.

1. **Amyotrophic Lateral Sclerosis.**—Both the upper and lower motor neurones are involved. There is atrophy of the anterior horns in the cord with great disappearance of the motor cells and wasting of the anterior nerve roots; the condition of the nerve roots should be compared with what is found in tabes. The remaining anterior horn cells show every degree of degeneration. The pyramidal tracts are degenerated, and there is a corresponding degeneration of the large Betz cells in the motor cortex. Late in the disease the motor nuclei in the pons and medulla degenerate. There is marked atrophy of the affected muscles. The change is spotty, not diffuse, many of the fibers being comparatively intact. These are innervated by the nerve cells which have escaped destruction. There is a replacement fibrosis.

The chief symptoms are weakness, wasting, and fibrillary tremors of the muscles. The amyotrophy begins in the small muscles of the hands (thenar, hypothenar and interossei), and spreads to the forearm and shoulder. Spasticity of the legs, exaggerated deep reflexes and a positive Babinski sign due to an upper motor neurone lesion may appear even earlier. Symptoms of bulbar paralysis (see below) complete the picture at the end. The patient seldom survives more than three years, death being due to bulbar paralysis.

2. **Progressive Muscular Atrophy.**—This is amyotrophic lateral sclerosis without clinical evidence of an upper motor neurone lesion, although at autopsy the lateral columns may show some degeneration. The disease is much rarer than the preceding form. The fibrillary tremors form the most striking feature of the clinical picture. As the bulbar centers are spared, the patient may drag out an existence for many years.

3. **Progressive Bulbar Palsy.**—The condition may be purely bulbar, or may be the end-stage of an amyotrophic lateral sclerosis. The motor nuclei of the pons and medulla are involved, *i. e.*, the seventh, ninth, tenth, eleventh and twelfth nerves. The clinical picture is best described by the alternative name, glosso-labio-pharyngeal paralysis. The first symptom is difficulty in articulation with loss of the labials. Owing to the weakness of the lips they are at first held in a peculiarly stiff manner; after a time the mouth remains permanently open. The tongue wastes and shows marked fibrillary tremors. There is paralysis of the palate and the pharynx, so that swallowing becomes impossible. The upper part of the face escapes.

**Little's Disease.**—The condition of *congenital spastic diplegia* is due to an upper motor neurone degeneration, or rather to an *agenesia* or failure of development on the part of the motor cortical cells and the pyramidal tracts. The convolutions in the motor area are small and atrophic (*microgyria*). There is an association with premature birth, but this is not a causal factor. The symptoms usually appear about a year after birth. The picture is purely motor. The child walks with a "cross-legged" or "scissors" gait, with great

spasticity of the legs. The deep reflexes are exaggerated and there is a double Babinski sign. There may be slight involvement of the arms.

**Spastic Cerebral Paralysis.**—Spastic cerebral paralysis or birth palsy is quite a different condition from Little's disease, and is due to a meningeal hemorrhage at the time of birth. A monoplegia or hemiplegia is commoner than diplegia, and the paralysis is evident soon after birth. A gross lesion is always present.

**Pick's Convolutional Atrophy.**—This is a very rare form of agnesia which manifests itself in the presenile period (fifty to sixty years). The brain is shrunken, and shows extreme symmetrical localized atrophy of parts of the cerebrum. The change is most marked in the frontal region, but in a case of the writer's the occipital convolutions were also extremely small. The atrophy is not arteriosclerotic or senile in character. The condition is progressive, and is accompanied by marked dementia. It is the phylogenetically younger parts of the brain which are most affected.

### SUBACUTE COMBINED DEGENERATION OF THE CORD

This nervous disease, characterized by paresthesias of the hands and feet and spastic paralysis of the legs, is closely related to pernicious anemia. Nearly every case sooner or later develops a macrocytic hyperchromic type of anemia, even though there may not be a full-fledged blood picture of pernicious anemia. In rare cases combined degeneration may complicate other conditions, such as leukemia and cancer of the stomach. The cord lesions are not due to the anemia, for nervous symptoms may develop long before there is any sign of anemia. They are due either to the deficiency responsible for the bone-marrow lesions, or to some other deficiency.

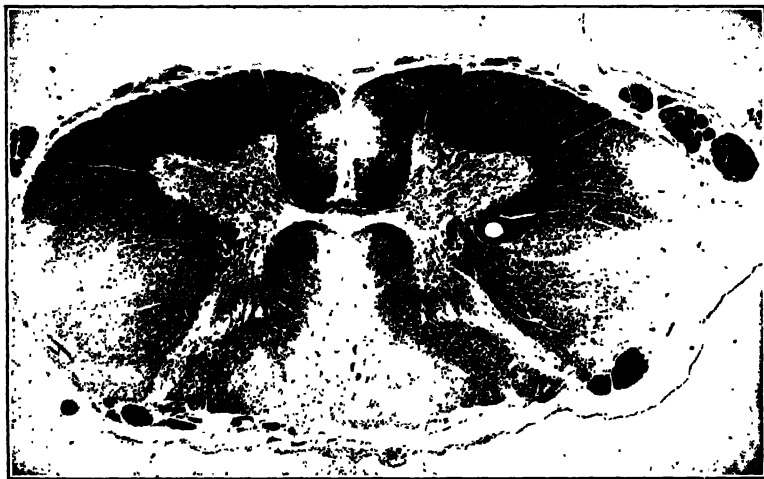


FIG 450.—Subacute combined degeneration of the cord. Marked degeneration in the posterior columns, the crossed pyramidal and direct pyramidal tracts, and the right indirect cerebellar tract. (Weigert's myelin stain.)  $\times 8$ .

**Lesions.**—These are most marked in the mid-dorsal region, with ascending secondary degeneration in the cervical cord and descending

secondary degeneration in the lumbar cord. The lesions are symmetrical, and involve the posterior columns, crossed and direct pyramidal tracts, and the cerebellar tracts. (Fig. 450.) In the early stage and in remissions they are confined to the dorsal columns. They can be seen as translucent patches with the naked eye. It is not a system disease; the lesions are formed by the fusion of many small patches. There is first demyelination with complete destruction of the medullary sheaths, followed later by disappearance of the axis cylinders. In the more recent lesions there is a complete absence of neuroglial proliferation, but in old lesions there may be some degree of secondary gliosis.

**The Relation of Symptoms to Lesions.**—There is exact correspondence between the lesions and symptoms. The earliest symptom is numbness and tingling at the tips of the fingers and toes, a feeling of "pins and needles." Later there may be sensory loss, ataxia, and loss of the sense of position. The knee-jerks may be lost. All of these are posterior column symptoms. In other cases there are lateral column symptoms, *i. e.*, spastic paralysis, exaggerated deep reflexes, and a double Babinski sign. The end-stage is one of flaccid paralysis with complete sensory loss and paralysis of the sphincters; this corresponds with disappearance of all the long tracts in the dorsal region.

### FRIEDREICH'S ATAXIA

This rare familial disease belongs to the group of the abiotrophics, in which slow degeneration of several of the tracts of the nervous system occurs without any obvious reason. It is a disease of the young. The distribution of the lesions resembles that in subacute combined degeneration, for the disease is a combined degeneration affecting both posterior and lateral columns. (Fig. 451.) Owing to the lesions in the posterior columns there is loss of the deep reflexes and of deep muscle sense, the latter partially accounting for the ataxia, which affects the arms as well as the legs. But there is a large cerebellar element in the ataxia ("cerebellar reel"), due to involvement of the direct cerebellar tract. Lesions in the pyramidal



FIG. 451.—Friedreich's ataxia.  $\times 7$ .

tracts cause muscular weakness and a positive Babinski sign, even though the knee jerks are lost. A characteristic deformity of the foot (high arch and hammer toe) and scoliosis are probably due to the pyramidal tract degeneration causing asymmetrical weakness of the muscles during the period of growth. Nystagmus and scanning speech are characteristic features, but their method of production is not obvious. Although posterior column sclerosis is present in both of the spinal ataxias (Friedreich's and locomotor), the former presents none of the lightning pains and other sensory disturbances which are so characteristic of tabes, a significant fact which suggests that the cause of these disturbances should be looked for outside the spinal cord.

## SYRINGOMYELIA

This is another rare disease of the earlier part of life depending on a perversion of development. It is therefore often associated with spina bifida and other congenital anomalies. The outstanding symptoms are dissociated anesthesia (loss of sensibility to pain and temperature with preservation of touch), muscular atrophy in the arms, a spastic condition of the legs, and certain so-called trophic lesions.

**Lesions.**—The essential lesion is a gliosis in the gray commissure and the base of the posterior horns in the lower cervical and upper dorsal region. This new-formed glial tissue becomes softened and liquefied so that a tubular cavity is formed (*syrinx*, a tube, the same word as syringe). (Fig 452.) The process may extend through the entire length of the cord, and even up into the brain stem. The cavity is separate from the central canals of the cord. The affected part is large, soft and flattened. The cavity is often lined by a layer of ependyma. It should be remembered that ependymal cells are merely specialized

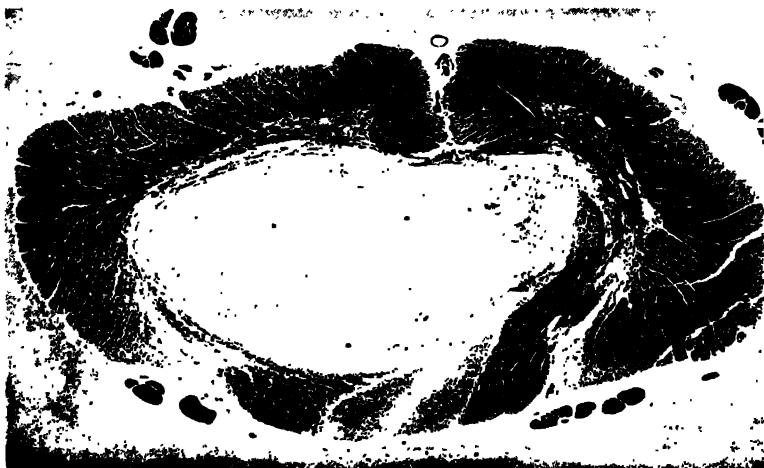


FIG. 452.—Syringomyelia. Marked cavity formation in the center of the cord, with surrounding zone of gliosis. (Weigert's myelin stain.)  $\times 8$ .

neuroglial cells, and that they may proliferate, giving rise to a gliosis, just as they may form an ependymal glioma. In the latter tumor the cells tend to surround tiny cavities, and it is possible that a similar tendency may explain the cavity formation in syringomyelia. All this is very theoretical, but there is nothing better to put in its place. We may regard the process, then, as a benign neoplasia of glial tissue, in which ependymal cells possibly play a prominent part.

**The Relation of Symptoms to Lesions.** The *dissociated anesthesia* is observed in the arms, as the lesion is commonly in the cervical cord. The fibers for pain and temperature cross in the gray commissure, and are therefore caught in the destructive process. Most of the touch fibers pass up in the posterior columns of the same side and therefore escape. This explains the dissociation of the anesthesia. *Spasticity* of the legs with some loss of power is due to pressure on the pyramidal tracts in the cervical region. In the arms there is *muscular atrophy* of the lower motor neurone type, similar to that seen in progressive muscular atrophy. As the pathological process seldom involves the anterior horns, the reason for this atrophy is obscure. The *trophic*

*lesions* are still more obscure. The name is unfortunate, for it is probable that the root of the trouble is not the cutting off of hypothetical trophic influences from the cord, but the anesthesia which permits the tissues to be unduly traumatized. Thus burns on the hands are of common occurrence, as the patient is insensitive to heat. The best known example is the *Charcot joint*, usually the shoulder or elbow. Its chief characteristic is its extreme painlessness, although the joint is completely disorganized and may become dislocated. Such an insensitive joint must receive much trauma against which there is now no protective mechanism, and this may lead to the remarkable disintegration characteristic of the condition.

**Hydromyelia.**—This is a simple dilatation of the central canal of the cord. It may affect the whole or only part of the canals. It may be associated with hydrocephalus, and is related to that condition rather than to syringomyelia.

### DISEASES OF THE CORPUS STRIATUM

The corpus striatum, so called because the fibers of the internal capsule traverse its gray matter, thus giving it a striated appearance, consists of the caudate nucleus and lenticular nucleus. The latter is divided into an outer part of recent origin, the putamen (neostriatum) and an inner more ancient part, the globus pallidus or pallidum (paleostriatum). A theoretical superstructure of considerable complexity has been reared on the basal ganglia. Fibers pass from the putamen to the globus pallidus, from there to the red nucleus and substantia nigra in the mid-brain, and on once more in the rubrospinal tract (extrapyramidal path) to the motor cells of the anterior horn of the cord. Some writers have ascribed different functions to the different parts of the corpus striatum and a correspondingly different symptomatology in disease. There is said to be a pallidal syndrome characterized by rigidity and tremor, and a neostriatal syndrome with choreiform and athetoid movements as a result of loss of inhibitory impulses from putamen and globus pallidus.

Kinnier Wilson in opposing this conception points out that the ganglia at the base of the brain still retain one of the great characteristics of basements, *viz.*, darkness. He considers that in man the corpus striatum exerts a steadying influence by way of the lenticulo-rubrospinal path (extrapyramidal path) on the innervation of the lower motor neurone from the pyramidal system. Both pyramidal and extrapyramidal influences play on the anterior horn cells, the resultant of these forces passing out along what Sherrington calls the final common path, *i. e.*, the lower motor neurone. If the steadying influences are removed from the final common path, tremor occurs, which is increased by any increase of pyramidal action.

The effects of disease of the corpus striatum are of three main types: (1) rigidity, (2) tremor, and (3) disorders of movement. The *rigidity* affects chiefly the large proximal muscles; the finer movements, such as those of the fingers are unimpaired. The apparent lack of emotional response, the mask-like face of Parkinsonism, is due to this rigidity. The *tremor* is seen in the non-rigid parts, *e. g.*, fingers, hands, tongue. It is due to rhythmical contraction of opposing muscles and is a release phenomenon; the striatal lesion either frees a lower center

to discharge rhythmic impulses, or removes a normal inhibition which restrains the cortical impulses playing on the anterior horn cells. Long ago Hughlings Jackson suggested that there was an intimate relation between tremor and rigidity: "Tremor is rigidity spread thin, and rigidity is tremor run together." The *disorders of movement* are mainly slowing and poverty. The slowing is largely due to the rigidity. There are no little movements, such as crossing one leg over the other, fingering the chin, etc. The final picture of striatal disease is one of complete motor helplessness, but there is no true paralysis.

**Paralysis Agitans.**—Parkinson's disease ("the shaking palsy") is a perfect example of disease of the extrapyramidal system, and will therefore be described in some detail. The clinical picture was drawn more than a hundred years ago by Parkinson with the hand of a master. The classical triad of symptoms are rigidity, tremor, and an attitude of flexion. (1) The *rigidity* results in a general absence of motor activity; there are none of the little movements already mentioned as depending on a healthy corpus striatum. It involves all the voluntary muscles, until at last the unhappy sufferer becomes as rigid as a block of marble. Articulation and swallowing become difficult, and finally there is complete anarthria and extreme dysphagia. The rigidity gives the face the familiar Parkinsonian mask. The mouth cannot be closed and the saliva drools down the chin. (2) The *tremor* affects the fingers and hands, giving a cigarette-rolling movement. It is present when the part is at rest, disappearing for a few minutes with movement. To use Parkinson's own words: "Commencing in one arm the wearisome agitation is borne until beyond sufferance, when by sudden changing of the posture it is for a time stopped in that limb." It is dependent on the integrity of the pyramidal tract for it disappears in a limb paralyzed as the result of a stroke, only to reappear as the power returns. (3) The whole attitude is one of *flexion*. The head is flexed on the chest, the body is bowed, the arms and wrists are flexed, the knees are bent. As the center of gravity is thrown forward he has to walk on the forepart of the feet, and comes to assume an overhanging position. "He is irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace." An advanced example of the disease can be diagnosed at a glance.

**Lesions.**—The lesions take the form of degenerative changes in the corpus striatum, especially disappearance of the large motor cells of the globus pallidus. More than this it is not possible to say. The changes are not confined to the globus pallidus, so that it is not justifiable to regard the condition as a pure syndrome of the globus pallidus. The cause of the degeneration is not known; possibly it is in the nature of a senile atrophy. Edema, degeneration, and fibrosis have been described in the muscle spindles (neuromuscular bundles) of the small muscles of the thumb. The rigidity and tremor are evidently the result of the lesions in the corpus striatum.



The possibility of a relation to trauma has been a matter of much dispute. Undoubtedly severe injury to the head may be followed after a latent interval by the appearance of tremors, due probably to destructive lesions in the basal ganglia caused by a wave of cerebrospinal fluid set up by the blow. These post-traumatic cases, however, do not present all the features of Parkinson's disease, and they may occur at a much earlier age.

**Post-encephalitic Paralysis Agitans.**—This condition, commonly called post-encephalitic Parkinsonism, presents the same clinical picture as that which has just been described, but the course is usually not progressive. In spite of this similarity it is not a corpus striatum disease, for the degenerative lesions are in the substantia nigra and the red nucleus. The pigmented cells of the former may largely disappear. It is therefore a disease of the extrapyramidal system.

**Progressive Lenticular Degeneration.**—This rare condition is also called hepato-lenticular degeneration and Wilson's disease. It is familial, affects young people, and is progressively fatal. The chief *clinical features* are muscular rigidity, tremor of the Parkinson type, difficulty with articulation, and marked emotionalism. There are always two entirely different *lesions*, as indicated by the name hepato-lenticular degeneration. The *first* is a degeneration of the lenticular nucleus, which may go on to softening and cavity formation. It is a pure striatal lesion, involving the caudate as well as the lenticular nucleus, but leaving the thalamus untouched. The *second* lesion is a cirrhosis of the liver of the Laennec type, although it never seems to give rise to symptoms of cirrhosis. The relationship between these two lesions is uncertain, but it may be noted that ligation of the common bile duct in the dog is followed by patchy cerebral degeneration, and that cirrhosis and other degenerative diseases of the liver in man may be associated with necrotic foci in the corpus striatum.

**Huntington's Chorea.**—This rare disease has an extremely marked hereditary tendency, but does not appear until middle life. The two chief *symptoms* are involuntary movements and tremors of choreiform character, and mental deterioration going on to dementia. Two *lesions* have been described: (1) atrophy of the cortical nerve cells and their associated fibers; (2) destruction and disappearance of the cells of the putamen and caudate nucleus (neostriatum) with comparative escape of the globus pallidus. The mental deterioration is evidently due to the extensive cortical changes, and the choreiform movements may be attributed to the loss of controlling influences from the neostriatum.

**Sydenham's Chorea.**—St. Vitus' dance is one of the commonest of nervous disorders, yet its pathology is still obscure. It usually occurs in girls, and nearly always before the age of twenty years. Chorea is a manifestation of rheumatic fever, but it may not be preceded by a definite arthritis, for rheumatic manifestations in childhood are not necessarily arthritic. The *symptoms* take the form of sudden, irregular, involuntary movements. The disease runs its course in a few weeks and rarely ends in death. The *lesions* in the fatal cases are remarkably insignificant. There is marked hyperemia, a moderate perivascular lymphocytosis, and slight degeneration of nerve cells. These changes are most marked in the cerebral cortex and the basal ganglia, especially the neostriatum.

## THE MUSCULAR DYSTROPHIES

This group of disorders of muscle is also called the myopathies, in the belief that the disease is of muscular origin. The cause of the condition is unknown. It has been shown experimentally in a variety of animals that a deficiency of vitamin E leads to necrosis of skeletal

muscle with hyalinization similar to that of Zenker's degeneration. The idea is gaining ground that the myopathies may be deficiency diseases, possibly acting through the sympathetic nervous system. The late J. J. Hunter considered that each skeletal muscle consists of two sets of fibers, each with its own nerve supply. The function of the fibers supplied by the sympathetic is a plastic one, responsible for fixation and the maintenance of posture. When this function is lost the picture is that of the muscular dystrophies. The lesions have the selective character which we associate with disease of the nervous system; some muscles may be profoundly affected, while a neighboring group may be quite normal. But the whole question is still in a highly theoretical stage.

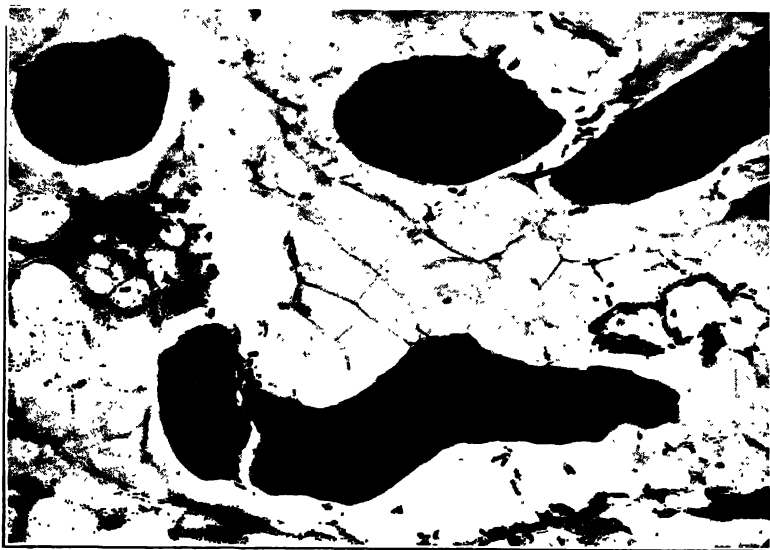


FIG. 453.—Pseudohypertrophic muscular dystrophy. The muscle fibers are swollen and are largely replaced by fat.  $\times 140$ .

The muscular dystrophies have several clinical divisions, but the basic pathology is the same. The disease begins in childhood, shows a very marked familial tendency so that several children in the family may be affected, attacks only the males, but is transmitted only by the females. The large muscles concerned with fixation (shoulder girdle, hip) are chiefly affected, the small muscles concerned with active movement (hand, etc.) usually escaping. This is the opposite to what occurs in progressive muscular atrophy. The largest group is known as *pseudohypertrophic muscular paralysis* because of a remarkable enlargement of the muscles of the calf or shoulder girdle. Although the muscles are enlarged, they are without power (all is not gold that glitters). The great symptom is muscular weakness. Owing to

paralysis of the gluteal muscles the patient cannot rise from the floor in the usual way, but has to "climb up his legs." The muscles of the shoulder girdle may be principally affected (*facio-scapulo-humeral type*).

**Lesions.**—These involve the muscles and interstitial tissue. In the common pseudohypertrophic form the muscles are large and firm; the gastrocnemius, deltoid, supraspinatus, and infraspinatus are most often affected. Other muscles are markedly atrophic. In the early stages the muscle fibers may be swollen, with loss of striations and increase of the sarcolemma nuclei, but later the fibers become atrophic. In this stage there may be a marked increase of the interstitial tissue, and great deposits of fat may occur between the muscle fibers. (Fig. 453). It is to these deposits of fat that most of the enlargement (pseudohypertrophy) is due. The exact cause of these deposits is not known, but indirect evidence suggests that they may be due to pituitary disturbance.

### INTRACRANIAL TUMORS

Tumors within the cranial cavity may be divided into two great groups, intracerebral and extracerebral. The intracerebral group comprise the gliomas, metastatic carcinoma, and a few miscellaneous tumors such as hemangioma. The extracerebral group, far more favorable from the surgical standpoint, comprise the meningiomas, acoustic neuromas, and tumors of the pituitary and craniopharyngiomas which have already been considered in connection with the pituitary body. All of these tumors may produce certain general effects, but these effects are most conveniently discussed with reference to the group of the gliomas.

Although gliomas are in many cases highly malignant tumors, they fail to produce metastases outside the central nervous system. The medulloblastoma shows a marked tendency to seeding throughout the subarachnoid space, both cerebral and spinal, and much less frequently on the walls of the ventricles. In rare instances the other forms of glioma may spread in a similar manner.

**General Effects.**—*Edema* is of common occurrence in the neighborhood of a brain tumor. Enlargement of the affected part, which is a constant accompaniment of tumor, may be largely due to the edema. *Secondary hydrocephalus* is perhaps the most important effect, for it is largely responsible for the increased intracranial pressure, and therefore for the classical (though late) symptoms of brain tumor, *i. e.*, headache, vomiting, and optic neuritis. Tumors in the posterior fossa are most likely to cause severe hydrocephalus, but a tumor in any position may produce some dilatation of the ventricles. A tumor in the posterior fossa may block the opening of the aqueduct of Sylvius or may press on the great vein of Galen as it curves around the splenium of the corpus callosum. This vein drains the choroid plexus, and pressure upon it leads to an increased production of cerebrospinal fluid and hydrocephalus. But a tumor in any part of the cranial cavity may cause hydrocephalus. This is probably due to pressure of the brain stem containing the narrow aqueduct of Sylvius against the hard edge of the tentorium cerebelli. *Distortion of the lateral ventricle* by the tumor is a common occurrence, and this can be detected by means of ventriculography, *i. e.*, filling the ventricles with air and taking

a roentgen-ray picture. The increased intracranial pressure causes flattening of the convolutions and obliteration of the subarachnoid space. At operation the brain may not show the normal pulsation. The *optic neuritis* is due to the fluid in the subarachnoid space being forced into the lymph spaces in the sheath of the optic nerve; this interferes with the venous return, and the result is edema and hemorrhage which give the ophthalmoscopic picture of choked disc and optic neuritis. When the intracranial pressure is high, clusters of arachnoid cells may penetrate the dura and appear on its cranial surface as nodular outgrowths. Hemorrhage into a glioma is common, and may cause a sudden exacerbation of symptoms or even death. The *skull* may show a characteristic mottling like beaten silver in the roentgen-ray picture from pressure of the convolutions, due to increased intracranial pressure. In meningioma there may be an even more characteristic local hyperostosis of the overlying bone.

The relation of trauma to glioma is a matter on which there is no uniformity of opinion. Some of those who have examined the statistics most carefully are of the opinion that no such relationship exists. The difficulty is to distinguish between mere coincidence and true causal relationship.

**Glioma.**—For practical purposes nearly all the tumors of the brain are neoplasms of the interstitial tissue, *i. e.*, gliomas. Of the three varieties of interstitial tissue, the microglia never gives rise to tumors, and the oligodendroglia very seldom does, so that practically all the gliomas arise from the astrocytes. The various intracranial tumors may be divided into a clinically benign group of slow growth and a much more malignant group. To the more benign group belong meningioma, acoustic nerve tumor, pituitary adenoma, cerebellar astrocytoma, ependymoma, bloodvessel tumors, and congenital tumors. The important members of the malignant group are glioblastoma, medulloblastoma and cerebral astrocytoma, although to a much less degree. It must be noted that although some of the gliomas are among the most malignant of tumors, they never give rise to metastases. This may be because the specialized glial tissue is unable to grow when transplanted to other organs. If large celloidin sections of the entire tumor and the surrounding brain tissue are made it will be found that in about one-third of the cases the glioma is relatively circumscribed, the microscopic limits corresponding fairly closely with the visible limits. About 60 per cent are diffuse, with microscopic limits extending widely beyond the grossly visible limits (Scherer). This is true of all cerebral astrocytomas. There may be multicentric growth, but this is practically confined to the glioblastomas. About 30 per cent of gliomas are bilateral.

Bailey and Cushing have divided the gliomas into a large number of subgroups, which differ markedly in their histological appearance and show a corresponding clinical difference in their prognosis. The basis of the classification is a histogenetic one. The primitive medullary epithelium gives rise to *spongioblasts*, which form the early spongework of the brain. The spongioblast develops a vascular process and sucker foot; it is then called an *astroblast*. The astroblast in turn develops fibrils and becomes an adult *astrocyte*. This is the main genealogical tree, but two other cells must be mentioned. Some of the spongio-

blasts collect around the lumen of the neural tube and become the *ependymal cells*. The *medulloblast* is a primitive undifferentiated cell which develops early from the medullary epithelium. Its subsequent fate is uncertain.

These various glial cells can be distinguished by means of the Spanish methods of gold and silver impregnation. A glioma may be constituted of any of these cells, and the tumor is named accordingly in Bailey and Cushing's classification. This does not mean that the tumor has originated from these cells; the cells of which it is composed have merely reverted to a more or less primitive type. The classification, indeed, is merely a method of grading. The most primitive and undifferentiated tumor, such as the medulloblastoma, belongs to Grade 4, while a well-differentiated tumor like the astrocytoma belongs to Grade 1. The types are not always pure and may be mixed. Surgical interference with an adult type may sometimes convert it into a rapidly-growing primitive type. Although the Spanish methods of staining have been invaluable for working out the different types, it must be understood that in the great majority of cases a correct diagnosis can be made with ordinary histological methods, especially when Mallory's phosphotungstic acid hematoxylin is used in addition, for by means of it the neuroglia fibrils can be stained sharply.

A large number of different forms of glioma have been described, but some of these are very rare and the identity of others is doubtful. We shall content ourselves with describing two common gliomas (glioblastoma and astrocytoma), two that are much less common (medulloblastoma and ependymoma), and merely mentioning a number of rarities.

A peculiar feature of the gliomas is that, no matter how malignant they may be, they do not metastasize outside the central nervous system. They make up for this, however, by showing a tendency to seeding throughout the subarachnoid space, both cerebral and spinal, a tendency which is much more marked in the case of the medulloblastoma.

**Glioblastoma Multiforme.**—This, the commonest and most malignant of the gliomas, is also called *spongioblastoma multiforme*, because the type cell is the spongioblast. It is a tumor of middle life, and is seldom found outside the cerebral hemispheres. It is not infrequently multiple—an unusual occurrence in a malignant tumor. If not treated, it rapidly kills the patient. The tumor is soft, gray, ill-defined, vascular, and often shows evidence of degeneration such as necrosis, hemorrhage, and cyst formation. Degeneration of the central part often gives the tumor a false appearance of encapsulation (Fig. 454); in reality it is highly invasive, and the surgeon's great difficulty is to know where the tumor ends and normal brain begins.

The *microscopic appearance* is characteristically varied. The tumor is highly cellular, and the cells are very pleomorphic, varying greatly in size and shape, recalling the varied cytological picture in osteogenic sarcoma of bone. This pleomorphism justifies the name "multiforme,"

which is applied to the common form of glioblastoma, in contrast to a rarer polar form of glioblastoma, in which the cells have a single process. Some of the cells are round or oval, some pear-shaped, some



FIG. 454.—Glioblastoma showing hemorrhage in center.

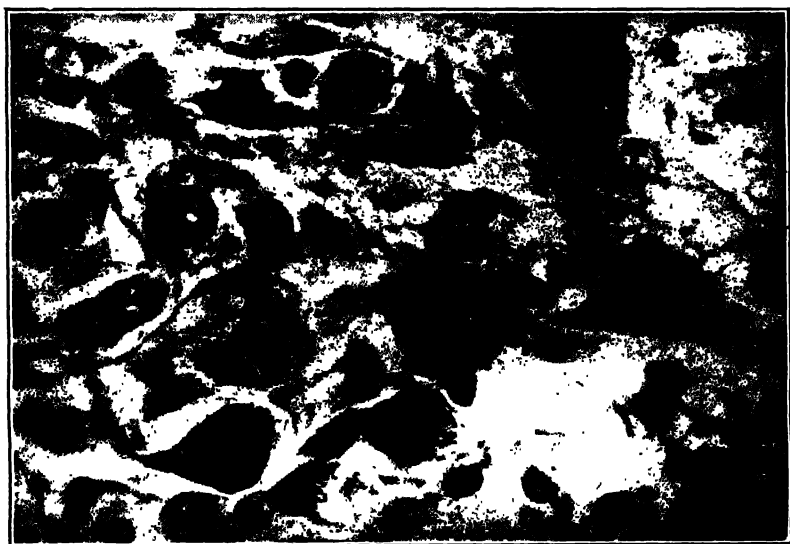


FIG. 455.—Glioblastoma multiforme. The cells vary greatly in shape: some are round, some are elongated, and some are pear-shaped.  $\times 700$ .

elongated. (Fig. 455.) They are bipolar spongioblasts when stained by Cajal's gold-sublimate method. There are also tumor giant cells with many nuclei. Mitoses are common. There are no glia fibers, for the spongioblast does not produce such fibers. The vascular endothelium often shows a remarkable proliferation so that the lumen of the vessels may be filled with masses of cells. This change may be observed in still normal tissue beyond the limits of the tumor. One can but guess at the significance of such a change. Around the tumor there is usually well-marked gliosis.

**Astrocytoma.** The astrocytoma is a comparatively benign tumor. The average time of survival after operation is six years (Cushing), and many of the patients appear to be completely cured. The tumor blends so gently with the surrounding tissue that no line of demarcation can be drawn. It is usually much firmer than the glioblastoma owing to the fibrils of which it is composed. The tumor may occur in any part of the brain. A common site is the cerebellum, especially in children. A distinction must be drawn between astrocytoma of the cerebrum in adults and astrocytoma of the cerebellum in children. The latter is the purest form of astrocytoma, often shows marked cyst formation, and is the most satisfactory glioma known to the surgeon. Most of the lesion may be represented by a cyst, with

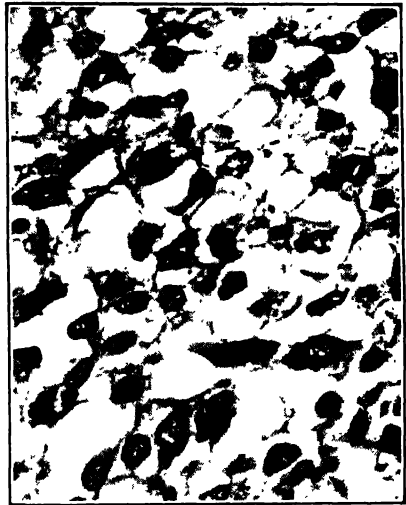


FIG. 456. Astrocytoma.  $\times 500$ .

only a small nubbin of tumor left in the wall. Small intraneoplastic cysts may be due to degeneration, but larger cysts, which are often outside the tumor, contain fluid which appears to be a transudate from the surface, and which rapidly accumulates after the cyst is aspirated. Astrocytoma of the cerebrum in adults may be much more cellular, and in places there may be an apparent transition towards glioblastoma.

The microscopic picture in a typical case forms a striking contrast to the glioblastoma. (Fig. 456.) The cells are few, and are uniform in size and shape. Sometimes, however, as the result of degenerative changes, there is swelling and hyalinization of the cell-body, and displacement of the nucleus to the side. (Fig. 457.) As already mentioned, in the cerebrum the tumor may be more cellular, and mitoses may occasionally be seen. The cells are separated by numerous glia fibrils, which are well stained with phosphotungstic acid hematoxylin, but are best shown by the gold method. (Fig. 458.) Neoplastic astrocytes, being often packed together, may be much more elongated

than those of the normal brain. Moreover they are often lacking in vascular footplates, which are always present in normal astrocytes. Bloodvessels are not numerous. A feature characteristic of astrocytoma is the survival of occasional nerve cells in the midst of the tumor; this must be attributed to lack of destructive power on the part of the tumor. Calcification is not uncommon, and may be seen in the roentgen-ray picture. There is no gliosis around the tumor, and it may be very hard to tell the limits of the growth.

**Medulloblastoma.**—This highly malignant and rapidly-growing tumor usually occurs in children in the mid-line of the cerebellum



FIG. 457.—Degenerated astrocytes in astrocytoma.  $\times 400$ .



FIG. 458.—Astrocytoma; Cajal's gold-sublimate method.  $\times 300$ .

(roof of fourth ventricle). It forms a soft reddish-gray mass which may fill the cavity of the fourth ventricle, producing marked hydrocephalus. It is the killing tumor of the child, just as glioblastoma is the killing tumor of the adult. In view of the fact that a tumor in the roof of the fourth ventricle of a child may be the extremely malignant medulloblastoma or the extremely innocent astrocytoma, biopsy confirmation of the tumor type is of great importance. The latter can be treated with complete success, whereas if the former is interfered with it is likely to be spread throughout the subarachnoid space. The medulloblastoma is the only glioma which penetrates the pia and invades the subarachnoid space diffusely. The *microscopic picture* is completely undifferentiated, like that of a round-cell sarcoma. The tumor is extremely cellular and there are no fibrils. The cells are round, but some may be carrot-shaped. The cells may be grouped around blood-



vessels, forming "pseudorosettes." These differ from the true rosettes of an ependymoma in having no lumen in the center.

**Ependymoma.**—This tumor is considerably more rare than the three preceding ones. It resembles the medulloblastoma in usually occurring in children and in the roof or floor of the fourth ventricle, but differs from it in being much less malignant and more highly differentiated. It may grow in the cerebrum close to the lateral or third ventricle. The tumor is fairly firm, and calcification, evident in the roentgen-ray picture, is quite common. *Microscopically* the tumor consists of ependymal cells or more primitive ependymal spongioblasts; the latter are tadpole-shaped, with an elongated tail. As the normal function of ependymal cells is to line a cavity, some of the tumor cells

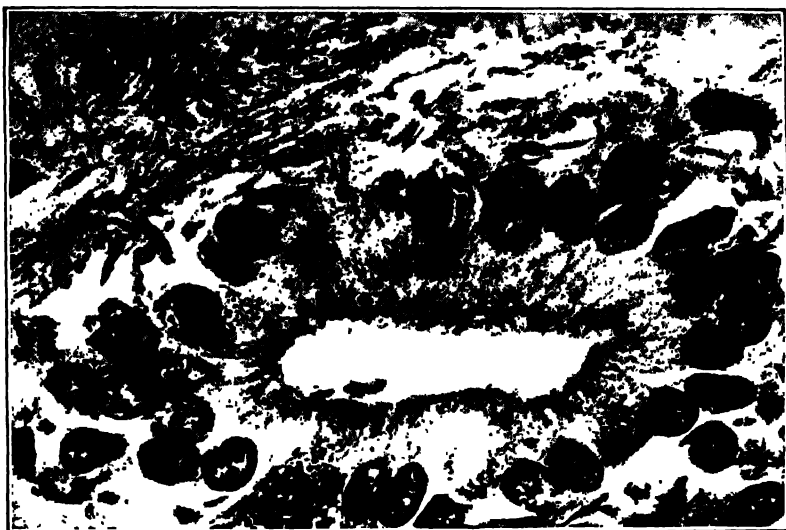


FIG. 459.—Ependymoma of fourth ventricle in a boy, aged two years. The tumor cells are grouped around a lumen. Blepharoplasts can be seen in the cytoplasm close to the lumen.  $\times 1000$ .

are grouped around small canals; these groups are known as rosettes, and when present in typical form are pathognomonic of ependymoma. (Fig. 459.) Between the nucleus and the lumen the cytoplasm may contain tiny rods known as blepharoplasts. These are characteristic of ependymal cells, being the remains of chromatin granules at the base of the cilia.

**Astroblastoma.**—A rare and relatively benign tumor composed of cells like astroblasts. The cells are attached to vessels by a large vascular process, and as these are not seen in ordinary preparations, the vessels seem to be surrounded by mantles of cells, but separated from them by a clear space.

**Oligodendroglioma.**—A very rare tumor of the oligodendroglia, confined to the cerebral hemispheres of adults. Although extremely cellular (Fig. 460), it is slowly growing, and shows a marked tendency to perivascular calcification

which can be recognized in the roentgen-ray picture. In ordinary sections the cell bodies are represented by clear spaces like vegetable cells. To prove the nature of the tumor the cell processes must be stained with silver.

**Pinealoma.**—This is another very rare tumor which grows from the pineal body. It occurs for the most part in the second decade, and is marked by symptoms of involvement of the corpora quadrigemina (oculomotor palsies,

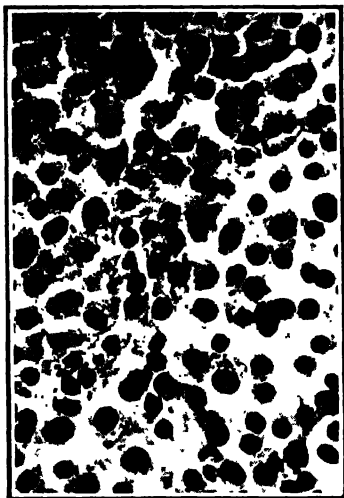


FIG. 460.—Oligodendroglioma.  
× 500.



FIG. 461.—Pinealoma. × 400.

deafness), and pubertas præcox, *i. e.*, precocious sexual development and adiposity. Hydrocephalus is marked owing to the position of the tumor. The tumor may be regarded as an “adenoma” of the pineal, for it consists of the two types of cells normally present, very large pineal cells and small round neuroglial cells. (Fig. 461).

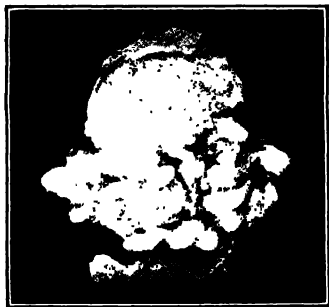


FIG. 462.—Pearly tumor (cholesteatoma).

**Cholesteatoma.** This rare tumor is of developmental origin, arising from epithelial implantations which occur in the development of the embryo. The common site is under the pia, but it may be in the substance of the brain or in one of the ventricles. Depending on the time that the cellular anlage is cut off, the capsule may be either purely epidermal or dermal with hair follicles. In the later case the tumor will be a *dermoid cyst* with the usual buttery contents and wisps of hair. In the much commoner epidermal form the lesion is covered by stratified epidermal cells, which become desquamated and cornified. The

gross appearance is highly characteristic, and has earned for the lesion the name of *pearly tumor*. (Fig. 462.) The tumor is globular, and the surface is smooth, silky, of a mother-of-pearl luster, and may present pea-sized elevations. The surface can be picked off in flakes. Microscopically the tumor consists of layers of polygonal cells filled with granules, fatty material, and cholesterol crystals.

**Ganglioneuroma.**—This is perhaps the rarest of brain tumors. It is composed of adult nerve cells, and is more likely to be found outside the brain, *e. g.*, in the adrenal medulla. (Fig. 135, page 299.)

**Retinoblastoma.**—This tumor is commonly called *glioma of the eye*, but it contains no glia fibers, and as it seems to develop from the retinal anlage of the embryo it seems better to call it a retinoblastoma. (Fig. 463.) Owing to the presence of "rosettes" of columnar cells, it has been regarded as a *neuro-epithelioma*. It is the second commonest tumor of the eye, malignant melanoma being the commonest. It is locally destructive, and in the later stages may metastasize to lymph nodes and internal organs, thus proving that it is not a glioma. The tumor consists of small round cells consisting of little more than nuclei, with hardly any cytoplasm and no fibrils. The rosettes when present are characteristic circular structures composed of columnar cells which probably have a tendency to develop into rods and cones. They are often absent. The tumor nearly always occurs before the fourth year, so that it may be regarded as of congenital origin; it is bilateral in 20 per cent of cases; it displays a remarkable and tragic familial tendency, 10 children out of 16 in one family having died of this tumor.

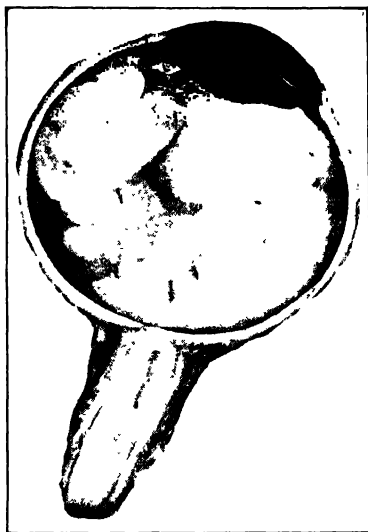


FIG. 463.—Retinoblastoma.

**Sheath Tumors.**—It has already been pointed out that it is convenient and logical to divide intracranial tumors (with the exception of pituitary tumors which have already been considered in Chapter XXVIII) into brain tumors proper and tumors of the sheaths of the brain. The latter comprise the meningioma and the acoustic nerve tumor.

**Meningioma.**—This is an innocent tumor (although rarely it may become malignant) and it constitutes one of the commonest forms of intracranial neoplasm. There is about one meningioma to every four gliomas. The term meningioma is hardly satisfactory from a histogenetic standpoint, but it has the advantage of being non-committal. It has been and still is called dural endothelioma, but it does not arise from the dura and is not an endothelioma. The tumor arises from groups of mesothelial cells which cover the arachnoid villi and the Pacchionian bodies, and may be regarded as a meningeal fibroblastoma. On account of their mode of origin the tumors are usually situated near the superior longitudinal sinus in the fronto-parietal region, but they may grow from the falx cerebri, or at the base of the skull in the anterior and middle cranial fossa.

The *gross appearance* is very characteristic, for the tumor presses on the brain from the outside and forms a deep bed for itself, from which in the autopsy room it can be readily shelled out. (Fig. 464.) In the operating room, however, things are far less simple, and the

surgeon may readily lose his patient from hemorrhage from large vessels which pass between the highly vascular overlying bone and the tumor. The meningioma is usually much firmer than the glioma.

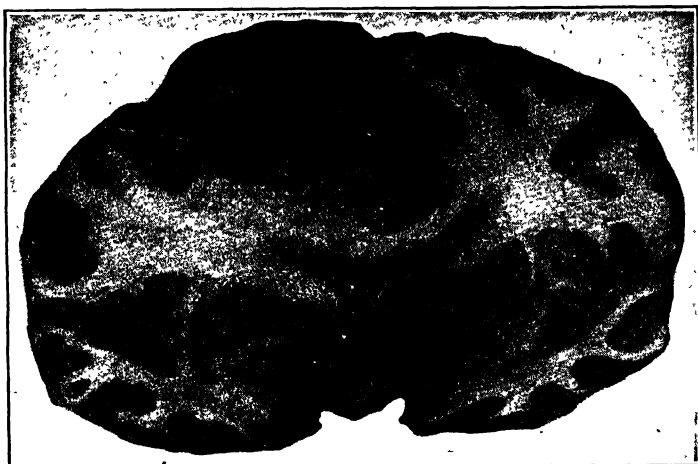


FIG. 464.—Meningioma. The tumor has formed a large depression for itself in the hemisphere, and has caused much distortion of the brain.

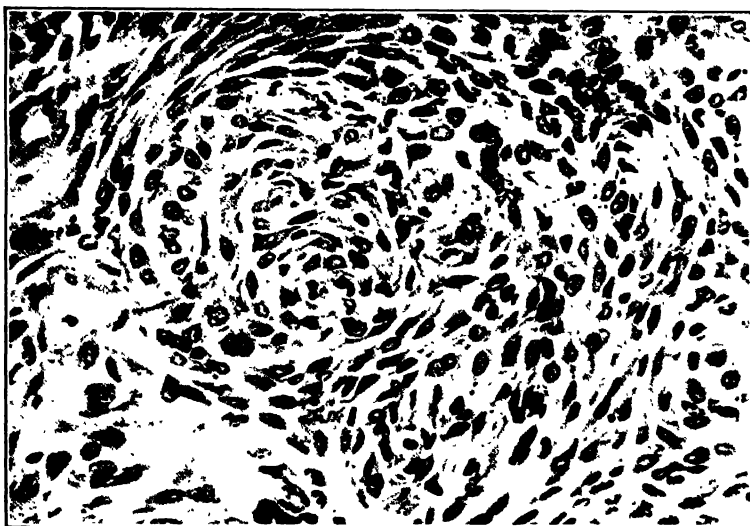


FIG. 465.—Meningioma. The whorled arrangement of the elongated cells is plainly shown.  $\times 400$ .

It is adherent externally to the dura. It remains encapsulated, and does not penetrate the pia nor infiltrate the brain, so that it lends itself to surgical removal. *Microscopically* it consists of elongated fibroblastic cells often showing a whorled arrangement. (Fig. 465.)

The whorls may undergo hyaline degeneration and form little masses like epithelial pearls. These may become calcified and resemble corpora amylacea, giving an appearance known as psammoma bodies or brain sand (*psammos*, sand), and on this account the tumor used to be known as a *psammoma*. In rapidly-growing tumors the cells may be rounder and much less differentiated. Occasionally fat may be present (*lipo-meningioma*). *Local changes in the skull* may be of great help in diagnosis. In about 25 per cent of cases there is bony thickening over the tumor which can be detected radiologically and sometimes clinically. This is due to penetration of the dura by the tumor and invasion of the skull, with ossification of the stroma of the invading tumor. In rare cases there may be erosion and perforation of the bone in place of thickening.

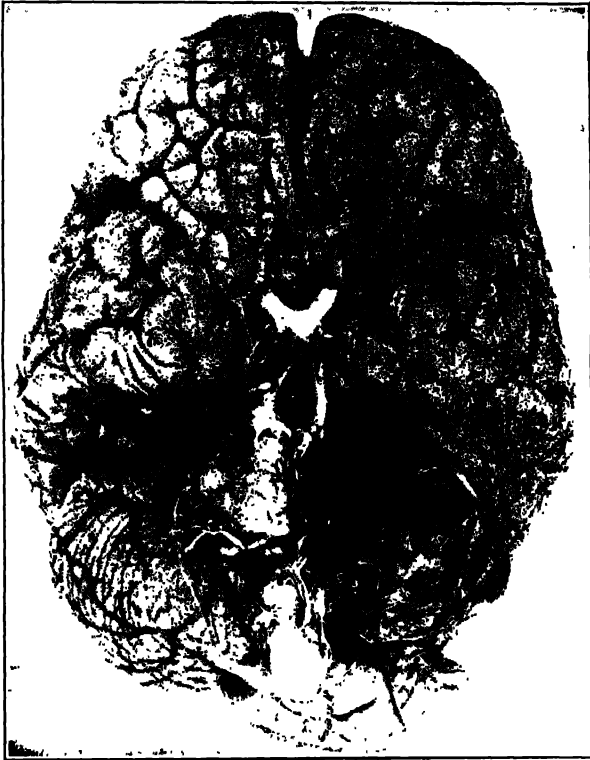


FIG. 466.—Acoustic nerve tumor. The tumor has produced marked distortion of the brain stem.

**Acoustic Nerve Tumor.**—This is the second of the sheath tumors, and it resembles the meningioma in many respects. Occurring in the cerebello-pontine angle and growing from the sheath of the acoustic nerve, it forms a firm, round, well-encapsulated tumor, which presses

on the brain stem and produces marked distortion and displacement of that structure. (Fig. 466.) A similar tumor sometimes grows on the roots of the spinal nerves. There is difference of opinion regarding the origin and nature of these tumors. It is usually regarded as a fibroblastoma arising from the perineurium of the nerve, but Masson believes that it is a tumor of the cells of the sheath of Schwann, what the French writers call a Schwannoma. It is identical in structure with the perineurial fibroblastomas (solitary neuromas) growing on peripheral nerves. The subject is discussed further in connection with tumors of nerves. *Microscopically* it consists of elongated nuclei often arranged side by side so as to produce a characteristic banded or "palisade" appearance. There may also be eddies or whorls of cells. The outline of the cells is vague, and the background is fibrous in character, probably collagen. The *clinical effects* are facial palsy and nerve deafness (seventh and eighth nerves), and the usual signs of intracranial tumor. An important feature is a nearly invariable increase of the protein in the cerebrospinal fluid, although in one of our cases it was normal. It can at least be said that a normal fluid in a posterior fossa tumor nearly always means an intracerebellar lesion. The protein increase may be attributed to blockage of the circulation of cerebrospinal fluid to the spinal subarachnoid space or to compression of the venous channels draining the choroid plexus.

**Hemangioma.**—Vascular tumors of the brain can be divided into (1) angiomatous malformations and (2) hemangioblastomas. Each group includes a general systemic disorder as well as the local cerebral lesion. The first condition is a cavernous angiomatosis of the brain; it is associated with a similar condition of the skin and with congenital glaucoma. The second is a capillary angiomatosis of the cerebellum and is associated with similar lesions of the retina and some of the viscera. The kidneys and the pancreas may be cystic. This angiomatosis of cerebellum and retina is known as *Lindau's disease*. It is hereditary in character, occurring in one family in three generations. Sometimes the lesions are in the medulla or cord instead of the cerebellum; they never occur in the cerebrum. The tumor is composed of angiomatous spaces between which are xanthoma-like cells filled with lipid.

**Secondary Tumors.**—When a diagnosis is made of tumor of the brain it must not be forgotten that the tumor may be secondary. The most common site of the primary tumor is the lung. In a series of 82 cases reviewed by Dr. Mary Tom in my department the percentage as regards the primary site was as follows: lung, 22; breast, 15; large intestine, 11; malignant melanoma, 8. The secondary tumors are often multiple. The course of the disease is apt to be more acute than in the case of a primary tumor. *Diffuse involvement of the meninges* may be the result of invasion of the subarachnoid space by a glioma (usually a medulloblastoma) or a secondary tumor (often a melanoma); sometimes the melanoma seems to originate in the meninges. A mantle of tumor cells may cover the brain and even the cord, and tumor cells may be found in the spinal fluid obtained by lumbar puncture.

### SPINAL CORD TUMORS

Tumors of the spinal cord are rare in comparison with tumors of the brain. The symptoms are of much longer duration, the history sometimes extending over a considerable number of years. The surgical prospect is much better than in the case of the brain, especially in the extramedullary tumors. The cord may be severely compressed, and yet when the tumor is removed function may return to an astonishing degree. The usual sequence of events, especially in extramedullary tumors, is first root pains, then the Brown-Séquard syndrome (paralysis of motion and deep sensation on the side of the tumor, loss of pain and temperature sense on the opposite side), and finally paralysis of the organic and deep reflexes. The *cerebrospinal fluid* may show the "compression syndrome" if the canal is blocked. In the cul-de-sac below the obstruction the characters of the fluid are as follows: (1) massive spontaneous coagulation; (2) xanthochromia or yellow coloration of the fluid; (3) marked increase in the protein; (4) no corresponding increase in the cells. This is known as the Froin syndrome, of which only the last two features may be present. The presence of a block can also be shown by the Queckenstedt sign (absence of the normal rise in spinal pressure when both jugular veins are compressed). The exact site may sometimes be determined by the intraspinal injection of lipiodol followed by radiography. The tumor may be extramedullary or intramedullary; the extramedullary tumors may be extradural or intradural.

**Extramedullary Tumors.**—These tumors are frequently benign in character, and there may be an interval of several years between the root symptoms and the appearance of any sign of pressure on the cord. Even when marked pressure has developed there may be little or no degeneration of the cord. Neurofibromas are the commonest, followed by meningiomas, and then by intramedullary tumors, of which the most frequent are ependymomas. *Extradural tumors* are uncommon. They are often sarcomatous in character, arising either from the outer surface of the dura or from the vertebrae. *Intradural tumors* form the main bulk of spinal cord tumors. The growth is usually benign in character, being either a meningioma or a perineurial fibroma of the nerve roots similar in character to the acoustic nerve tumor (possibly a Schwannoma). The tumor is usually oval, seldom grows to a large size, and shows absence of the normal cord pulsation. The cord may be seriously compressed, but is seldom invaded by the tumor.

**Intramedullary Tumors.**—These tumors are gliomas. Practically all the forms which have been described as occurring in the brain may be found in the cord. Perhaps the commonest is the ependymoma, which arises from the ependymal cells of the central canal. The tumor extends up and down the cord rather than horizontally, and the overlying dura may appear normal. Absence of pulsation indicates the lesion when the surgeon opens the spinal canal.

## THE NERVES

**Injury and Repair.**—The effects of injury can be best studied in section of a peripheral nerve. Attention may be confined to one of the individual fibers of which the nerve is composed. When a nerve fiber is divided from its cell of origin the distal part undergoes the changes known as Wallerian degeneration, which have already been described in connection with the general pathology of the nervous system. It will be recalled that all three components of the fiber share in these changes. The axis cylinder disintegrates and disappears, the medullary sheath breaks up into droplets of myelin, and the cells of the sheath of Schwann proliferate and exert a phagocytic action on the degenerated myelin. Similar changes occur in the proximal part up to the first node of Ranvier.

But combined with the degenerative changes there is soon evidence of attempts at *repair*, just as inflammation of any tissue may pass imperceptibly into regeneration. The proliferated Schwann cells in both proximal and distal ends become arranged in the form of a tube along which new axis cylinders may grow out once more to the periphery. For long there was great difference of opinion as to whether the regeneration was *peripheral*, the new fibers being laid down by the Schwann cells (neurilemma) and joining up later with the proximal end, or *central*, the new fibers being formed as outgrowths from the divided proximal end. Modern opinion is entirely in favor of the central view, but it must be admitted that it is sometimes difficult to account for the speedy return of function which may follow division of a nerve on the hypothesis that the new fibers have grown from the site of the lesion to the motor or sensory end-organ concerned.

In the course of a few days the axis cylinder proceeds to grow out as a bulbous process in search of the missing distal end. This search will be unsuccessful if the distance between the two ends is more than an inch, or if the ends are separated by scar tissue. The surgeon may transplant a piece of nerve to close the gap when it is unduly large, but this piece merely acts as a bridge along which the new fibers may travel to the distal part. When the bulbous end of the axis cylinder reaches the distal portion it puts out fine fibrils which grow down the tubular sheath formed by the proliferated Schwann cells. These fibrils reestablish the continuity of the pathway and become clothed again, with the assistance of the Schwann ends, by a medullary sheath. If the distance is too great to be bridged or if the part supplied by the nerve has been amputated, the axis cylinders may coil up so as to form a nodule capped by fibrous tissue. Such a mass at the end of a nerve, composed of nervous and fibrous tissue, is called an *amputation neuroma* (stump neuroma). Some degree of sensation may reappear fairly quickly, but complete restoration of function, even when the cut ends are brought into accurate apposition, seldom occurs in less than three or four months.

The process which has just been described is only seen in the peri-



pheral nerves. In the central nervous system the fibers do not possess a sheath of Schwann, so that while Wallerian degeneration takes place as before, real repair is impossible.

**Neuritis.**—The term neuritis signifies inflammation, but the lesions are for the most part degenerative rather than inflammatory. Direct infection of a nerve produces true inflammation known as *interstitial neuritis*, and likely to be confined to a single nerve. The degenerative form is known as *toxic neuritis*, because it may be caused by diffusely acting toxins. It is therefore frequently multiple, and is known clinically as *multiple peripheral neuritis* or *polyneuritis*.

Polyneuritis can be produced experimentally by means of a diet deficient in vitamin B<sub>1</sub>. Similar lesions are seen in cases of human avitaminosis, such as beri-beri. It is probable that dietary deficiency is a commoner cause of polyneuritis than was formerly believed. For instance alcoholic neuritis is now thought to be due to avitaminosis caused by chronic gastritis and consequent interference with digestion. Such cases might better be called polyneuropathy than polyneuritis.

**Toxic Neuritis.**—The toxins which cause this common form of neuritis may be inorganic or organic. A long list of poisons could be given, but the more important ones are lead, arsenic, alcohol, (avitaminosis), diphtheria toxin, and some metabolic poison produced in diabetes. Neuritis may follow septic conditions and many of the infectious fevers. In some cases no cause can be found. It is the small nerve twigs which are affected first and to the greatest degree, so that the term peripheral neuritis is well chosen. As the nerve is traced upward the condition becomes progressively less. The changes are similar to those of Wallerian degeneration following division of a nerve, but are less severe and complete. The axis cylinders degenerate and may show varicose swellings, but they do not disappear. The medullary sheath breaks up into droplets of myelin. (Fig. 467.) The Schwann cells proliferate and become phagocytic for the degenerating myelin. The muscle fibers supplied by the degenerated nerve show fatty and other retrogressive changes. As the nerve degeneration is seldom complete, recovery is the rule. But if the action of the toxin is long-continued, the interstitial connective tissue may proliferate and may replace the nerve fibers, with permanent impairment of function. The *symptoms* depend on the type of nerve affected. There may be paralysis and wasting of muscles (dropped wrist and dropped foot in alcoholic or lead neuritis), anesthesia, incoördination, loss of reflexes, and trophic disturbances.

**Interstitial Neuritis.**—This form of neuritis is usually caused by bacterial invasion of the nerve from some neighboring septic focus, so that the distribution is asymmetrical, although more than one nerve may be involved. Other forms of irritant are cold, which is a common cause of facial nerve paralysis (Bell's palsy), and pressure from a crutch. The nerve is swollen and red. The interstitial tissue is congested and infiltrated with leucocytes, or may show little beyond edema. The exudate may be confined to the sheath of the nerve. The medullary

sheaths of the fibers may undergo some secondary degeneration, but the axis cylinders preserve their integrity, so that when the pressure of the exudate is withdrawn there is restoration of function. The Schwann cells proliferate and take on a phagocytic function.



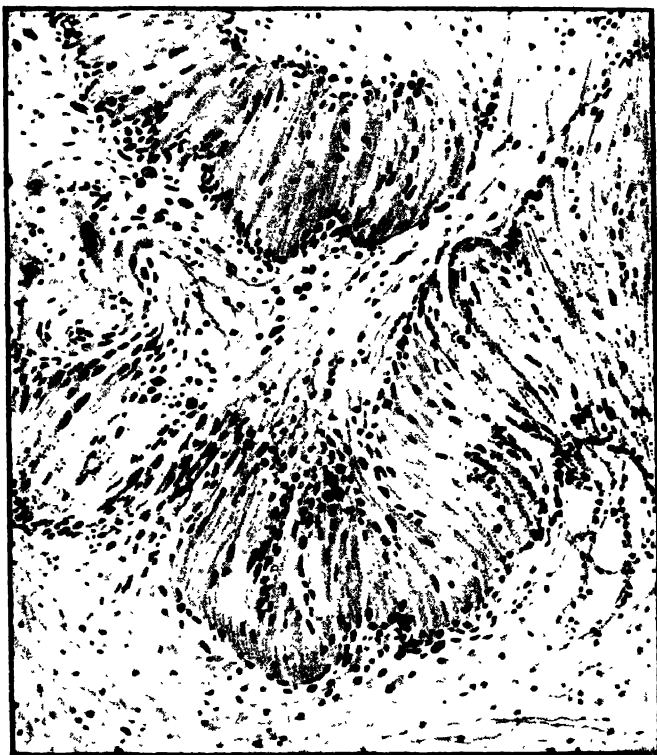
FIG. 467. — Demyelination in toxic neuritis.  $\times 510$ .



FIG. 468. — Neurofibroma (Schwannoma) showing palisading of nuclei.  $\times 225$ .

**Tumors.**—The tumors of nerves form a remarkably confusing and complex subject regarding which a large amount might be said without adding very much to the reader's knowledge. Newer staining methods and increased knowledge of nerve histology should have brought better understanding, but they have served rather to make confusion worse confounded. "The histology of the nerve trunk seems quite simple and well understood if one reads but a single authoritative paper on the subject, but should one read several it will take on more and more complexity" (Foot). The chief cleavage of opinion is as to which constituent of the nerve the neurinoma or ordinary nerve tumor arises from. This is commonly believed to be the connective tissue of the perineurium (Mallory, Penfield), and the tumor is, therefore, called perineurial fibroma or fibroblastoma. On the other hand Masson and other members of the French school maintain that it arises from the cells of the sheath of Schwann, and call it a Schwann-

PLATE XXIX



**Neurofibroma**

Marked palisade arrangement of the cells. (Masson's trichrome green.)



oma. This cleavage may be illustrated by the fact that in 1940 Tarlov published a paper proving that by a special silver technique it was possible to differentiate the fibroblasts of the nerve from the Schwann cells, and that only fibroblasts were present in neurinomas which are, therefore, perineurial fibroblastomas, whereas in the very next paper in the same journal Murray and Stout, employing tissue culture technique to differentiate the two types of cells, proved that the tumors are Schwannomas! Disregarding controversy and employing generally accepted terms the following main types may be recognized: (1) neurofibroma (perineurial fibroma, neurinoma, Schwannoma) a conventional name indicating a nerve tumor resembling a fibroma without regard to its cell of origin; (2) neurofibromatosis (von Recklinghausen's disease); (3) neurogenic sarcoma, and (4) nerve nevus.

No matter which view may be adopted, an examination of the different tumors will show the following common features: long, slender, wire-like fibers with elongated nuclei which have a tendency to be arranged in parallel or palisade fashion (Plate XXIX and Fig. 468); in addition to the palisading, which always suggests a nerve sheath origin, the nuclei may be grouped in eddies and streams. The more benign the tumor, the more pronounced are these features. The palisading is perhaps best seen in the acoustic nerve tumor and the similar tumors which occur in the spinal nerve roots, while the whorls are characteristic of meningioma. In the more malignant forms these characters tend to be lost. Penfield and Young have recently recorded a case of multiple neurofibromata, acoustic nerve tumor, similar tumors on several of the other cranial nerves, and multiple meningiomas.

**Neurofibroma.**—This is a benign tumor which forms a round or fusiform firm white mass on the course of one of the larger nerves. It is attached to the sheath of the nerve, but the nerve fibers are not incorporated in the tumor, so that the term perineurial fibroma appears to be justified. *Microscopically* it is composed of long slender cells, the elongated nuclei of which are arranged in palisades or show whorls and eddies. This structure is identical with that of the acoustic nerve tumor, which also is a perineurial fibroma.

**Neurofibromatosis (Von Recklinghausen's Disease).**—In this peculiar and often familial condition there are large numbers of tumors, sometimes several hundreds of them, growing from the fine cutaneous nerves, so that the condition is also known as multiple neurofibromata. They form soft nodules in the skin (*molluscum fibrosum*), and may be distributed over the entire body. The skin is often pigmented in patches, or there may be groups of brown spots like freckles. This is of great interest in relation to the nervous origin of nævi (see below). Moreover some members of a family may develop nerve tumors, while others only have spots of pigment. Peculiar soft overgrowths of connective tissue may occur, causing great enlargement of a limb, a form of elephantiasis. It is probable that the terrible deformities of the Elephant Man in Treves' story were due to this cause. Megacolon, giant appendix, and other similar overgrowths have been described

in connection with similar lesions of the visceral nerves. It seems justifiable to regard the condition as more of a connective-tissue reaction that is part of a general process than as a simple tumor, neurofibromatosis rather than neurofibroma. Acoustic nerve tumor and meningioma may be associated with the condition, and there is always some intermingling of perineurial fibromatous tissue. *Microscopically* the same general picture is seen once again, but the structure is much more mixed. The characteristic tissue has a tangled or reticular structure, which suggests a malformation rather than a neoplasm; this tissue does not show palisading or whorls. It often undergoes a jelly-like hyaline degeneration. Superimposed on this reticular tissue is a varying amount of tissue of neurofibromatous type with palisades and whorls. When special stains are used nerve fibrils can be seen passing through the mass; this never occurs in a neurofibroma. It would appear that in von Recklinghausen's disease all the elements composing the nerve are involved in some degree, possibly due to failure of the insulating function of the sheath of Schwann.

Although multiple neurofibromas occur especially on the cutaneous nerves, they are also found on the deeper and visceral nerves as well as on the cranial nerves. These deeper growths are prone to undergo sarcomatous change, and this is a frequent cause of death in von Recklinghausen's disease. Sometimes there is a diffuse neurofibromatosis with widespread overgrowth of the endoneurium and separation of the nerve fibers, a condition known as *plexiform neuroma*. This usually occurs in the head and neck, especially in the distribution of the fifth cranial and upper cervical nerves. Sometimes the main nerve trunks are involved, a condition which is often familial and to which the misleading name of *familial hypertrophic neuritis* has been given in the past.

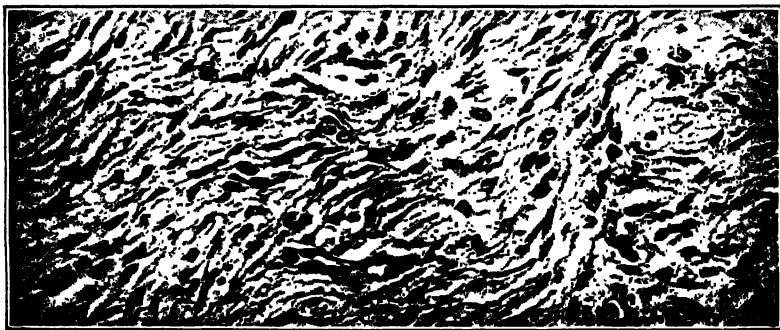


FIG. 469.—Neurogenic sarcoma showing the fasciculated arrangement.  $\times 300$ .

**Neurogenic Sarcoma.**—Malignant tumors may arise from neurofibromas and from neurofibromatosis. Ewing and other members of the Memorial Hospital group also believe that the great majority of what have formerly been regarded as fibrosarcomas of the soft

parts are derived from nerve sheaths and should be called neurogenic sarcomas, although no connection with nerves may be demonstrable. They form single, slowly-growing, infiltrating tumors, usually in the subcutaneous and intermuscular tissue of the arm and leg, the commonest location being the thigh. More rarely they occur in the viscera. *Microscopically* the tumor consists of elongated cells or fibers arranged in interlacing bundles and whorls showing a "curly" arrangement, in contrast to the parallel disposition of the fibers of a fibroma, an appearance always suggestive of a neurogenic origin. (Fig. 469.) There is not the palisading of a neurofibroma, the cells are more swollen, and there may be mitotic figures.

**Nerve Nævus.**—We have already seen in Chapter X that the nævus and malignant melanoma of the skin are most probably derived from specialized sensory end-organs. The neurogenic origin of the pigmented tumors is of interest in view of the frequent occurrence of patches of pigmentation in multiple neurofibromatosis.

## DEFECTS OF DEVELOPMENT OF THE NERVOUS SYSTEM

**Brain.**—*Anencephaly* is a condition in which the cranial vault is deficient and practically the entire brain is missing with the exception of some nervous tissue at the base of the posterior cranial fossa. The spinal cord may be absent except for some flattened plates of nerve tissue, yet the nerves are well developed, as is the body in general. The explanation of this is not evident. There is a remarkable atrophy of the adrenal cortex in the anencephalic monster; the nature of this atrophy is discussed in Chapter XXVIII. The condition is incompatible with life. There may be a deficiency in the skull, usually in the line of a suture, with protrusion of the contents of the cranial cavity. A protrusion of the meninges is called a *meningocele*, which is a sac filled with cerebrospinal fluid and communicating with the subarachnoid space. An *encephalocele* is a protrusion of the brain substance, a condition often associated with and dependent upon hydrocephalus. *Microcephaly* is a condition in which the brain, usually the cerebral hemispheres, remains small. The convolutions may not develop, a condition of *microgyria*. *Porencephaly* is a lack of development of a superficial part of a hemisphere; the resulting space is filled with fluid, covered by membranes, and usually communicates with the lateral ventricle.

*Amaurotic family idiocy* may be mentioned here, as it is essentially a congenital defect. It is also known as Tay-Sach's disease, is congenital in character, and confined to Hebrew infants. The first-born are rarely affected, but when one child has had the disease the subsequent children seldom escape. The symptoms are idiocy, muscular weakness, and rapidly developing blindness (amaurosis), so that the disease is well named. There is a characteristic cherry-red spot at the macula. The brain is small and hard. There is widespread degeneration of the cells and fibers of the cerebral cortex, the anterior and posterior horns of the cord, and the posterior root ganglia. The affected cells both in the brain and in the retina are filled with lipid (Fig. 470), so this is really a lipid storage condition and may be regarded as a variety of Niemann-Pick's disease. *Tuberous sclerosis* is a congenital condition in which tumor-like masses of neuroglia are scattered through the brain. The glial cells are chiefly large astrocytes. The condition is often associated with congenital malformations in other organs. *Hydrocephalus* is commoner than any of the above conditions, but it has already been described earlier in this chapter.

**Spinal Cord.**—The spinal canal may remain entirely open especially in the lumbar region, a condition known as *rhachischisis* and often associated with anencephaly. *Spina bifida* is a much more common and important condition, in which the neural arches remain open, but the canal is closed by the soft



FIG. 470.—Amaurotic family idiocy. The cortical nerve cells are greatly distended with lipoid, which displaces the nucleus to one side.  $\times 375$ .

parts. The contents of the canal are protruded under the skin to form a soft mass which at once calls attention to the condition. Sometimes there is no protrusion and swelling to indicate the defect, so that the lesion is hidden, a condition known as *spina bifida occulta*. Its presence is indicated by a patch of hair on the wrinkled skin covering the defect; this hair may resemble a small tail. As the lower part of the canal is the last to close, spina bifida is commonest in the lumbo-sacral region. As a rule five or six vertebrae are involved, sometimes only one. The condition occurs about once in every 1000 births. The contents of the sac may be of three varieties: (1) meningo-myelocele, (2) meningocele, (3) syringomyelocele. In the *meningo-myelocele* (myelocele), which is the common form, the cord and the nerves of the cauda equina are spread out on the wall of the sac to which they are attached, producing a dimple of the skin known as the umbilicus. In the *meningocele*, which usually occurs in the

sacral region, the sac is formed by a hernial protrusion of the arachnoid, the cord or cauda equina remaining within the vertebral canal. The *syringomyelocele* is a rare form in which there is great distention of the central canal and thinning of the cord tissue, so that the wall of the sac is the wall of the canal and is lined by ependymal cells. Spina bifida is often associated with congenital hydrocephalus. *Sacro-coccygeal tumors* of developmental origin occur at the lower end of the spinal canal. Some of these are true teratomata, containing well-formed adult tissue. Dermoid tumors, lipomas and cysts may be present either inside or outside the canal. Other tumors appear to arise from remains of the neurenteric canal. Or these remains may be represented by a depression over the tip of the coccyx (the "postanal dimple"), or by a channel lined by skin furnished with hair, sweat and sebaceous glands, and known as the *pilonidal sinus*, pilonidal meaning a nest of hair. The chief *symptoms* are paralysis of the bladder and rectum, weakness in the muscles of the legs leading to clubfoot, trophic ulcers, etc.; these are caused by pressure on the nerve centers. In spina bifida occulta the symptoms appear to be due to a fibrous cord stretching from the skin through the vertebral defect to be attached to the termination of the cord. As the vertebral column grows faster than the cord, it is evident that there will be an increasing degree of traction on the cord with the production of symptoms which may be very puzzling until the defect is discovered.



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## CHAPTER XXXII

### THE BONES

**Descriptive Outline.**—In describing disease in bone the following structures should be considered: periosteum, shaft, medullary cavity, epiphyscal cartilages (if still present), epiphyses, and articular cartilage. The bone-marrow varies in different bones and at different ages. In childhood all the marrow is red, but with the approach of adult life the red becomes converted into yellow marrow in the shaft of the long bones. The marrow of the flat bones (skull, sternum, ribs, vertebræ and pelvis) remains red.

### THE PHYSIOLOGY OF BONE

The anatomy of bone is a commonplace subject with which everyone is acquainted. The physiology of bone is a little less familiar. Bone does not serve merely as a rigid support. It is the great calcium and phosphorus reserve of the body, a reserve which is being continually drawn upon or added to, so that its structure is not fixed and permanent. It is composed of living cells and hyaline matrix impregnated with calcium salts. The vital character of bone is illustrated by the words of Sir Charles Bell, written more than a hundred years ago: "Scrape a bone and its vessels bleed; cut or bore a bone and its granulations sprout up; break a bone and it will heal; burn it and it dies." The cells are of two kinds: (1) Adult bone cells lodged in lacunar spaces surrounded by matrix; (2) osteoblasts, *i. e.*, osteogenic cells of a specific nature but not completely differentiated, which form a more or less continuous investment for the bone in the deep layer of the periosteum, in the Haversian canals, and in the endosteum. Most of the tissues contain about 6 mg. of calcium per 100 cc., but in bone the figure rises to 10,000 mg. The normal blood calcium varies from 9 to 11 mg., with an average of 10 mg. Under normal conditions a state of equilibrium exists between the calcium in the blood and that in the bones, but in disease it may be seriously disturbed. The calcium is absorbed from the food in the small intestine, and is excreted by the large intestine and to a lesser extent by the kidney. The calcium in the bone is combined with phosphorus in the form of calcium phosphate, which constitutes 80 per cent of the mineral content of the matrix, the remainder consisting of calcium carbonate and magnesium phosphate.

The complex problem of *ossification* will not be discussed here. It may be said, however, that it is becoming increasingly evident that the deposition of calcium and phosphorus in the osteoid tissue which is the precursor of true bone is a physico-chemical process in which the physico-chemical nature of the matrix is a factor of great im-

portance. This is shown by the experiment of Wells, who transplanted boiled cartilage from one animal into the tissues of another animal, and found that the transplanted material, though dead, soon became calcified. A second factor which determines the laying down of calcium salts is the action of *phosphatase*, an enzyme which hydrolyzes the phosphoric esters into inorganic phosphates. This enzyme is produced by the bone cells, but is most abundant in young growing bones and in the layer immediately below the periosteum which is rich in osteoblasts. It is not present in young cartilage until a center of ossification appears. The much-debated question as to the part which the periosteum plays in bone formation will be discussed in connection with the repair of a fracture. Sometimes *metaplastic ossification* (to be distinguished from metastatic calcification) may occur, owing to a tissue other than osteoid becoming transformed into bone. In this way there may be bone formation in the walls of arteries, in the scars of abdominal wounds, and in the tonsil. It is hard to find a satisfactory explanation of this process.

*Calcification* is the term applied to the deposition of calcium in tissue which is not osteoid. The process is discussed at length in Chapter II. *Metastatic calcification* occurs when calcium is removed from the bones as the result of some rarefying process and is deposited in other tissues. Hyperparathyroidism affords one of the best examples.

**Absorption of Bone.**—There is no tissue in the body which is capable of so much overgrowth or on the other hand so much absorption as bone. The cause of the absorption may be general (hyperparathyroidism) or local (pressure, etc.). It occurs in old age, from disuse, as the result of acute and chronic inflammation, and due to tumor and aneurism. The removal of the excess callus of a fracture and of a sequestrum (dead bone) are excellent examples. Bone undergoing absorption is softer, more easily cut, and bleeds more readily because of its greater vascularity. It can be recognized in the roentgen-ray picture by the decreased density of the shadow.

There are two chief factors in the absorption of bone: (1) vascular absorption, and (2) the action of osteoclasts. (1) *Vascular absorption* is the powerful factor. In ordinary compact bone the bloodvessels run longitudinally in a series of channels called the Haversian canals, around which the bony lamellæ are grouped, and transversely from the periosteum in Volkmann's canals. Persistent vascular dilatation is followed by widening of the canals at the expense of the bone, and if inflammatory granulation tissue is formed within them, as in tuberculosis, the absorption becomes very marked, a condition of *rarefaction* or *osteoporosis*. Primary removal of the calcium salts, as in hyperparathyroidism, is also followed by widening of the canals and the formation of granulation tissue within them, but these changes have now become effects rather than causes of the absorption of bone. This primary removal of calcium is known as *halisteresis* (*hals*, salt; *steresis*, privation) or osteolysis. It would appear that in primary vascular resorption the mechanism by which the calcium is removed

and the canals widened is a physico-chemical one. In inflammation there are probably local changes in the hydrogen-ion concentration that lead to solution of calcium and the production of narrow zones of decalcification around the vessels which allow the vascular canals to become dilated. Any local excessive production of carbon dioxide tends to cause solution of calcium, for the solubility is affected directly by the carbon dioxide tension of the blood and tissue fluids. The reaction which takes place at the line of contact of dead and living bone is of this nature, although inflammation is also a factor here. For these reasons only well-vascularized living bone can be absorbed quickly. Dead bone is absorbed slowly by osteoclasts.

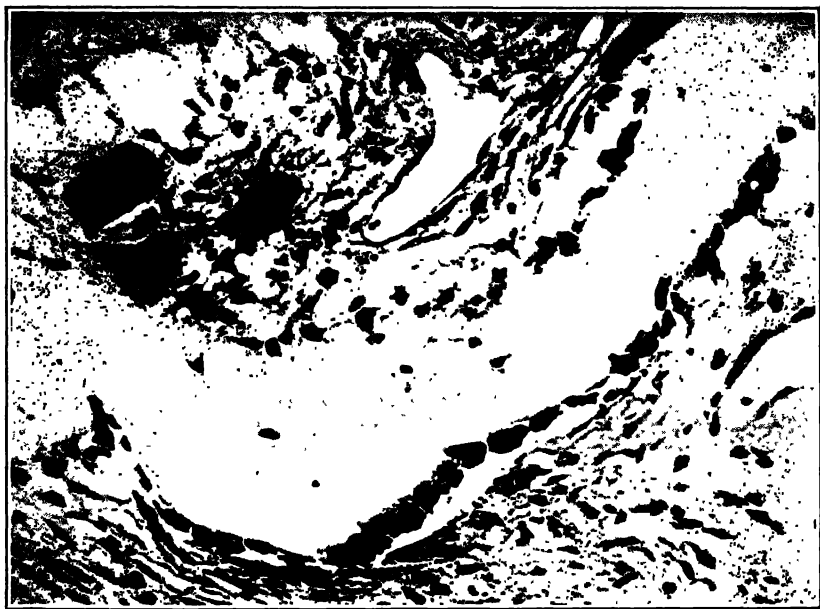


FIG. 471.—Three multinucleated osteoclasts above and to the left of a bone trabecula, the lower margin of which is lined by osteoblasts.  $\times 300$ .

(2) *Osteoclasts* may be absent or they may dominate the process. The osteoclast or bone phagocyte is a large cell with strongly acidophilic and granular cytoplasm; it is often multinucleated, containing a few or a large number of nuclei. (Fig. 471.) It is from the osteoclasts that the foreign body giant cells of bone are derived. It may show a fringed or toothed border (brush border) along the edge in contact with bone. Howship's lacunæ on the surface under the periosteum are produced by the osteoclasts. The phagocytic action of osteoclasts is most readily studied in the removal of small fragments of bone which have become separated. Large foreign body giant cells are formed for this purpose. It is probable that decalcification must first occur before

the osteoclast can exert its phagocytic action. This chemical change is brought about by the tissue juices, possibly by the osteoclasts themselves.

There may be too little bone either because bone resorption is too great (osteitis fibrosa) or because there is deficient deposition of bone. The latter may be due to failure of the osteoblasts to lay down an organic matrix (osteoporosis) or to failure in deposition of calcium in this matrix (osteomalacia). Osteoporosis often occurs from disuse, as the stresses and strains of action seem to stimulate the fibroblasts. In old age osteoblastic activity flags, giving senile osteoporosis. Osteoporosis is often seen in women after the menopause, at a time when the body is no longer liable to be called upon to form bone for babies; this may be called post-menopausal osteoporosis (Albright *et al.*).

Owing to the readiness with which bone formation and bone absorption can occur, a *remodelling of bone* is continually taking place. Bone tissue is very sensitive to demands made upon it and responds readily to these demands. It is hardly too much to say that every change in the function of a bone is followed by definite changes in its internal architecture. As the result of a fracture the lines of stress in a bone may change as if it was one of the most plastic of structures.

Reference may be made here to the novel views on the physiology and pathology of bone formation which have been advanced by Leriche and Policard, and which are well summarized in Greig's book on *The Surgical Pathology of Bone*. According to these observers bone formation is preceded by the formation of a young mesenchymal tissue which they call an ossifiable medium. In this medium there is deposited a firm, highly refractile, homogeneous material, the preosseous substance, and it is in this substance that calcium is deposited from the surrounding lymph. For ossification to occur two requisites are necessary: (1) an adequate blood supply, and (2) an adequate supply of calcium. Thus it is the local circulatory adjustments which are all-important; the activity of osteoblasts is not essential. This view serves to explain the heterotopic or metastatic formation of bone in connective tissue where no osteoblasts are present. Leriche, and Policard emphasize the importance of circulatory disturbances in modifying the structure of bone. Hyperemia is followed by decalcification and osteoporosis, lessened circulation by osteosclerosis, and loss of blood supply by necrosis. In a fracture the destruction of cells liberates stimulating substances such as histamine and acetylcholine; these cause local hyperemia, which in turn leads to rarefaction and the removal of spicules and sharp edges of bone. The hyperemia subsides, fibrous tissue formation still further diminishes the blood supply, and the new bone which is formed becomes denser than normal. The chief value of a bone graft is to supply the abundance of local calcium which is necessary for the formation of new bone.

**Repair of Bone.**—The repair of bone is best studied in the healing of a fracture, either in human material or in experimental fractures in animals. Adult bone cells have lost the power of proliferation so that they play no part in the regeneration of bone. Repair is carried out entirely by the osteoblasts which line the deep layer of the periosteum, the endosteum, and the Haversian canals. The deep cellular layer of the periosteum is a striking structure which must be seen to be

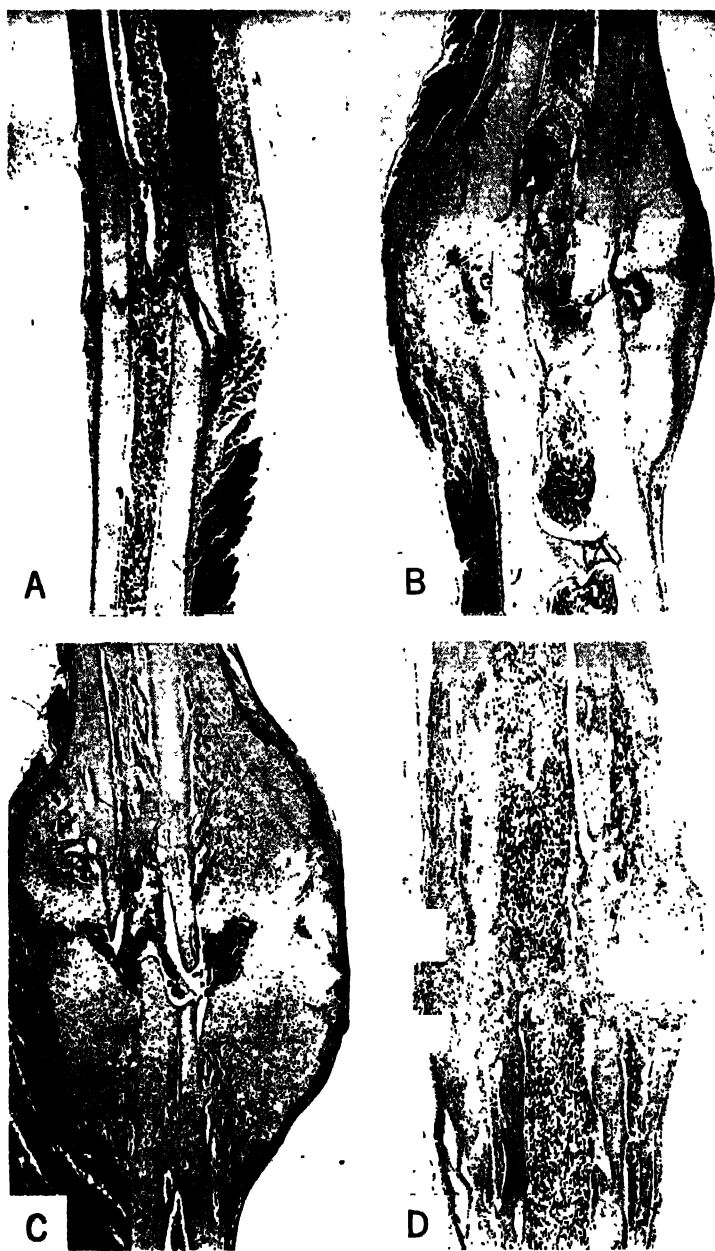


FIG. 472.—Healing of experimental fractures.  $\times 14$ . *A*, Three days (subperiosteal osteoblasts); *B*, seven days (osteoid); *C*, fifteen days (abundant callus); *D*, six weeks (diminished callus being converted into bone). (Boyd, Surgical Pathology, courtesy of W. B. Saunders Company.)



appreciated. It is much more abundant in young bone, and can be seen to react exuberantly after a fracture. Osteoblasts are present both in the periosteum and the surface layer of bone, so that repair can occur either with or without the periosteum. The essential function of the periosteum is to supply the outer part of the bone with blood. Removal or separation of the periosteum is apt to be followed by death of this part of the bone.

*Healing of a Fracture.*—This takes place in three stages: First *granulation tissue* forms in the exudate between the broken ends of bone then *osteoid tissue* is formed, and finally *calcium salts* are deposited with the production of bone. (1) As a result of the fracture, blood and a varying amount of exudate are poured out between and around the ends of bone. This is invaded by cells and new capillaries, and a kind of granulation tissue is produced. The proliferating cells are osteoblasts, derived for the most part from the deep layer of the periosteum. The proliferation of osteoblasts is of an extraordinarily rapid and massive character; indeed, there is no other non-malignant process which is quite comparable with it. (Fig. 472, A.) (2) In the course of four or five days the osteoblasts form trabeculae around central spaces which become Haversian canals. This is osteoid tissue, *i. e.*, tissue resembling bone in its structural arrangement but with no calcium salts in its homogeneous matrix. (Fig. 472, B.) The osteoid tissue, also known as *callus*, becomes increased in amount so as to act as a splint. By the end of the second week it is remarkably abundant. (Fig. 472, C.) (3) Finally calcium is laid down, and the ends are knit together by rigid, fully formed bone. (Fig. 472, D.) Low blood calcium produced by deficient diet does not slow the rate of healing or lead to non-union. In the immediate neighborhood of the fracture the bone cells die. Near the fracture the osteogenic cells proliferate in massive fashion, and may form cartilage instead of bone. This cartilage formation is most marked when there is movement or separation of the fragments. The new cartilage is invaded and replaced by bone. This is ossification in cartilage, as compared with the process just described which corresponds to ossification in membrane.

The new material formed at the site of the fracture is known as *callus* on account of its hardness. In the later stages it may become calcified, but at first it is osteoid in character. Some of it is *external*, ensheathing the broken ends like solder; some is *intermediate*, forming a direct union between the fractured surfaces; some is *internal*, filling the marrow cavity. The internal and external callus is removed by osteoclasts, and the bone undergoes a process of molding which goes on for months, and results in a rearrangement of the lamellae to meet the new stresses. If the gap between the fragments is not bridged by osteogenic cells in a certain time, fibroblasts will fill the gap with fibrous tissue the matrix of which has no special affinity for calcium salts (non-union or fibrous union).

*Fate of a Bone Graft.*—When a piece of bone is transplanted to another position the greater part of it dies. Dead bone can be easily

recognized under the microscope from the shrivelled appearance of the bone cells and the fact that large numbers of the lacunæ are empty. The part of bone bathed by the body fluids remains alive, *i. e.*, the surface, the lining of the medullary cavity, and the Haversian canals. The cells in these places are osteoblasts, so that osteoblastic activity is soon apparent. But much more striking, especially in the earlier stages, is bone removal. New vessels from the surrounding tissue grow along the Haversian canals, so that the bone becomes revascularized and is at the same time absorbed. Multinucleated osteoclasts also attack the graft, and many foreign body giant cells may be formed. The removal of the graft is gradually brought about by the two great processes already studied, *i. e.*, vascular absorption and osteoclastic activity. In the course of six months if the graft has no function to perform it is merely represented by an atrophic mass of fibrous tissue. On the other hand if it becomes a functioning structure, as when it is in continuity with another bone, osteoblastic activity is combined with absorption, and gradually it becomes the dominant process. The graft may finally become converted into living healthy bone. If the graft is taken from an animal of another species, none of the osteoblasts will survive.

### ACUTE OSTEOMYELITIS

The term osteomyelitis indicates inflammation of bone and bone-marrow. But it is really an inflammation of the soft parts of bone, *i. e.*, the contents of the medullary cavity and the Haversian canals, together with the periosteum. It is a boil in a bone. The calcified portion takes no active part in the process, but it suffers secondarily from the loss of blood supply, and a greater or less portion may die.

**Etiology.**—Osteomyelitis may be: (1) hematogenous, or (2) non-hematogenous in origin. In the non-hematogenous form the infection may come (*a*) from without, or (*b*) by extension. In *children* and adolescents (those with growing bones) osteomyelitis is due to a hematogenous infection. The common infecting organism is *Staphylococcus aureus*. Next in frequency come *Staphylococcus albus*, *Streptococcus pyogenes*, *Pneumococcus* (especially in babies and young children), *Bacillus coli*, and *Bacillus typhosus*. The staphylococcus often enters the blood stream through the skin, and it is common to find a healing boil if the whole body is carefully examined. In other cases the throat, teeth, and tonsils may be suspected. *Trauma* is often given as a predisposing cause, but this is so common in a young boy that it is difficult to be sure of its significance.

In *adults* hematogenous infection is rare. When it does occur the disease is much less acute. Infection is most likely to be introduced from without, as in a compound fracture, gunshot wound, etc. In *children* also the infection may be local in origin, as in osteomyelitis of the mandible from an infected tooth, or inflammation of the mastoid process from middle-ear suppuration.

**Symptoms.**—Acute hematogenous osteomyelitis is a disease of children, commonest in boys in the second decade. It is a disease of growing bones, rarely seen in the adult. It commences with the signs of an acute infection, *i. e.*, chills, high fever, rapid pulse, leucocytosis, and positive blood culture. There is severe pain and tenderness at the end of one of the long bones, together with redness, swelling, and edema. Death may occur from septicemia or pyemia (endocarditis, abscesses in the kidneys, etc.), or if treatment is inadequate, the disease may become chronic. As the initial lesions are confined to the soft parts of the bone, there are no characteristic roentgen-ray changes in the earlier stages of the disease.

**Lesions.**—In this description of the lesions it is presumed that we are dealing with the hematogenous osteomyelitis of children. The bones most often affected are the femur and tibia (much exposed to trauma and strain), followed by the humerus. The infection starts in the metaphysis—the part of the shaft which borders on the epiphyseal line in a growing bone. This region possesses a peculiarly rich blood supply, and the branches of the nutrient artery end in sharp hair-pin bends in which clumps of bacteria are readily arrested. It can be shown experimentally that this is the part of the bone which suffers most in sudden twists and strains. In adults the disease may start in any part of the bone.

The initial lesion is a focal suppuration (abscess) of the cancellous bone at the end of the shaft. Infection *spreads* rapidly in two directions: (1) along the medullary cavity, and (2) outward to the cortex. Pus is formed beneath the periosteum and lifts that membrane from the bone, at the same time making its way along the outside of the shaft. From there it may penetrate the Volkmann canals which run at right angles to the surface, and thus infect the marrow at lower levels, so that the central infection may be spotty in character. Owing to the inflammatory swelling there is a great increase of tension within the rigid walls of the cancellous spaces and the Haversian canals, so that the vessels are compressed and their lumen obliterated. Many of the vessels are found to be thrombosed, and the septic thrombi form the chief menace of osteomyelitis, namely the formation of pyemic abscesses throughout the body. These three factors, the raising of the periosteum from the bone which it supplies with blood, the increased tension and vascular compression within the bony canals, and the thrombosis have one effect in common: they cut off the blood supply from the calcified part of the bone, with the result that a varying portion of the shaft dies. The denuded surface of dead bone has an opaque white appearance and does not bleed when scraped. The fatty tissue of the marrow is destroyed and is converted into an oily pus. The *adjacent joint* is often filled with a sterile serous effusion. Sometimes the infection may pass to the epiphysis, perforate the articular cartilage, and invade the joint, setting up a suppurative arthritis.

The dead bone becomes separated from the living by the action of osteoclasts, forming a *sequestrum*, which can be lifted out freely when it is exposed at operation. But in the meanwhile the periosteum is not

inactive. Although it is separated from the bone, some of the cells of the osteogenic layer usually survive, and when the acuteness of the infection is past these osteoblasts lay down new bone over the sequestrum in the form of a *new case* or *involucrum*. A mild septic infection always acts as a powerful periosteal stimulant, and the vigorous osteogenesis may be indicated by the presence of spicules and processes of bone on the surface. If the infection is very severe, all the osteoblasts may be destroyed, so that no new bone is formed. The involucrum is perforated here and there by *cloacæ* or sewers through which passes the pus produced by the irritation of the dead bone. (Fig. 473.)



FIG. 473.—Osteomyelitis of upper end of tibia showing new bone formation and cloacæ.

Nature is unable to deal with this state of affairs, and the dead shaft remains locked up within the rigid involucrum without any chance of being absorbed. Without surgical interference this stage may last indefinitely. Amyloid disease may develop after a time as a result of the long-continued suppuration. Bones developed in membrane, *e. g.*, flat bones of the skull and upper jaw, are not reproduced to any extent.

Osteomyelitis due to *hemolytic streptococci* differs in several respects from the usual staphylococcal form. Sequestrum formation is rare. There is no chronic phase of the disease, nor does the infection reappear later in other bones, so that the prognosis is much better. The flat bones are often involved.

*Osteomyelitis of the spine* usually commences in the neural arches of the vertebræ, although in the cervical region it is more likely to start in the vertebral bodies. When it begins in the neural arches the pus spreads backward, when it begins in the bodies it spreads forward, and may cause a retropharyngeal abscess. Death is likely to result from septic meningitis.

**The Relation of Symptoms to Lesions.**—The chief symptoms of acute osteomyelitis is pain and tenderness at the end of one of the long bones. This is due to the extreme tension within the unyielding bone caused by the violent inflammation. The septicemic and pyemic symptoms are explained by the readiness with which the infected material and septic thrombi pass from the sinusoids of the marrow into the veins and the general circulation.

**Chronic Osteomyelitis.**—If acute osteomyelitis is not adequately treated, *i. e.*, if the focus of suppuration is merely incised, the condition may become

chronic and drag on until the patient dies of amyloid disease. But it may be more or less chronic from the beginning, with no definite history of an acute attack. Such a condition is known as a *Brodie's abscess*, a chronic circumscribed focus of suppuration at the upper end of the tibia, lower end of femur, upper end of humerus, and occasionally elsewhere. During periods of quiescence there is a small cavity surrounded by dense bone and containing a little serous fluid, but during periodic exacerbations the cavity is filled with pus from which staphylococci may be isolated. *Typhoid osteomyelitis* is a chronic infection which usually appears about two months after the acute illness, but there may be an interval of several years. The bacilli have been isolated twenty years after the original infection. The upper end of the tibia, the ribs and the sternum are the common sites.

**Non-suppurative Epiphysitis.**—Of recent years a group of cases has come to be recognized, in which there is a quiet necrosis of the epiphysis of a bone in young children. The best recognized form is that known as *Legg-Perthes' disease*, an osteochondritis deformans affecting the head of the femur, but *Köhler's disease* of the scaphoid and *Kienboch's disease* of the os lunatum belong to the same group. The center of ossification of the head of the femur, scaphoid, etc., is broken down and necrotic, so that several small sequestra may be formed, but without any pus. The condition is probably the result of a very low-grade infection, which clears up in time, so that complete spontaneous recovery is the rule. In Legg-Perthes' disease there is a remarkable flattening of the head of the femur, the neck being stunted and thick, giving a roentgen-ray picture from which a diagnosis can readily be made. Limp is the chief symptom, and there is usually little or no pain.

## TUBERCULOSIS OF BONE

Tuberculosis of bone is a chronic osteomyelitis occurring in early life, displaying an excess of bone destruction over bone formation, yet with a tendency toward limitation of spread and spontaneous healing. The disease begins in spongy bone, and is commonest in the vertebræ, the small bones of the hands and feet, and the ends of the long bones including both metaphysis and epiphysis. As in the case of acute osteomyelitis, the region of the knee (lower end of femur and upper end of tibia) is a common site. There may be more than one focus; in the vertebral column this is the rule, not the exception. The infection is usually hematogenous, being carried to the spongy bone by the blood stream from a distant focus in lung, lymph nodes, etc., although occasionally no evident focus can be found. The infection is bovine in type in about 20 per cent of cases of all ages. In children the percentage is considerably higher. Trauma probably plays a part in inducing the bacilli to settle down, as can be shown experimentally, but the trauma must be mild. A severe injury such as a fracture calls forth such a rapid reparative reaction that the bacilli have no chance to establish themselves. Sometimes the infection spreads from a joint to the epiphysis by way of the perivascular lymphatics. Bone and joint tuberculosis are often associated; the primary lesion may be in either structure.

**Lesions.**—The lesions are of two main types: (1) There may be little or no caseation, but an abundant formation of soft tuberculous granulation tissue. (Fig. 474.) This exerts an erosive action, as a result of which the Haversian canals are enlarged and the outer and inner

surfaces of the bone are eaten away. Osteoclasts assist in the work of destruction; but it is not a wholesale destruction. Branching trabeculae of bone are left, the interspaces being filled with granulation tissue. This is a process of rarefaction or osteoporosis to which the name of *caries* is given. (2) There may be marked softening, destruction of bony trabeculae, and caseation, which may be followed by the formation of tuberculous pus and a cold abscess. This type of lesion is characteristically seen in tuberculosis of the vertebrae. Although the lesions of tuberculosis are essentially destructive there may be a limited amount of osteosclerosis and formation of new bone. The periosteal osteogenic activity characteristic of osteomyelitis is never seen in tuberculosis, unless a septic element has been superadded.



FIG. 474.—Tuberculous granulation tissue causing erosion of bone. Several giant cells can be seen.

The infection may spread down the medullary cavity so that most of the shaft is involved. It may spread through the epiphyseal cartilage, or if it starts in the epiphysis it may perforate the articular cartilage and invade the joint; the articular cartilage may be completely separated from the underlying bone. It may spread to the periosteum, where it forms a subperiosteal abscess. The soft parts then become involved, with the formation of a cold abscess which discharges through a sinus on to the skin.

*Tuberculous dactylitis* is a condition in which a metacarpal or one of the phalanges develops a fusiform swelling as a result of diffuse involvement of the medulla. The interior of the shaft is absorbed and new bone is laid down on the surface by the periosteum, so that the shaft appears to be expanded.

*Tuberculosis of the Vertebrae*.—This is also known as Pott's disease of the spine. The vertebrae are the commonest bones affected by tuberculosis. The disease occurs especially in young children, and usually begins in the center of the body of a vertebra which is supplied by a branch of the posterior spinal artery. Discrete lesions are often present in several adjoining vertebrae. The center of the bone becomes caseous and the disease spreads to and destroys the intervertebral discs, but spares the transverse processes, spines, and articular processes. The destruction of the discs is of special importance, because in secondary carcinoma of the vertebrae, which often presents a radio-

logical picture very similar to that of tuberculosis, the discs are hardly ever involved. The bodies collapse in front, while the spines remain intact behind, so that an acute curvature develops with its convexity pointing backward. (Fig. 475.) In the rather rare *peripheral* form of adults the disease is confined to the anterior surface of the vertebræ, an area supplied by branches from the intercostal arteries; there is little or no deformity, but a large number of vertebræ may be involved. (Fig. 476.)



FIG. 475

FIG. 475.—The central form of tuberculosis of the spine. The body of one vertebra is destroyed and collapsed, causing backward curvature of the spine.

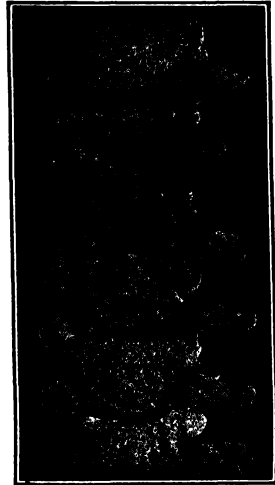


FIG. 476

FIG. 476.—Peripheral form of tuberculosis of the spine with surface involvement of many of the vertebral bodies.

In children there is usually evidence of pressure on the cord. This is not due to the angling of the spine, but to the formation of tuberculous granulation tissue or to an accumulation of pus under the posterior common ligament which presses on the cord. It is remarkable how even severe pressure symptoms such as paraplegia may clear up when the weight is taken off the spine.

A *cold abscess* often develops and this may trek in almost any direction, although it is unable to travel directly backward owing to the posterior common ligament. It soon escapes at the sides of the vertebræ, and is then free to travel at will. In the *cervical* region it may form a retropharyngeal abscess or may appear at the side of the neck. In the *dorsal* region it may spread along a rib; when it comes to the surface it is very liable to be mistaken for primary disease of the rib unless the spine is carefully examined. In the *lumbar* region the pus enters the sheath of the psoas muscle, and passes down as a psoas abscess into the iliac fossa and under Poupart's ligament; it may then

point at the saphenous opening or may pass down the thigh as far as the popliteal space. The pus may enter the sheath of the iliacus instead of the psoas; it will then point above Poupárt's ligament. In any of these cites mistakes in diagnosis are frequent. When the abscess discharges on the surface a mixed infection develops, and the clinical picture changes very much for the worse with hectic temperature and rapid wasting. Amyloid disease may now develop, or the patient may die of general miliary tuberculosis.

The *course* of the disease varies. As the spine is seldom at rest there is a strong tendency to progression. If the patient is kept absolutely at rest on his back under the best hygienic conditions an astonishing recovery may follow with firm fibrous union between the vertebræ.

### SYPHILIS OF BONE

Syphilitic disease of bone is an inflammation, an osteitis, just as tuberculosis is a special form of inflammation. It differs from tuberculosis in the following respects: (1) it affects the diaphysis of long bones rather than the articular ends, (2) the joint is seldom involved, and (3) osteosclerosis with new-bone formation is much more prominent than osteoporosis or rarefaction. The bones most commonly affected are the tibia, sternum, cranium, and the bones of the face, especially the nose and palate. The disease may be of the acquired or congenital form. The lesions may appear in the earlier or the later stages. In the earlier stages there is likely to be a periostitis; in the late stages gummatous formation is not uncommon. The two common manifestations of bone syphilis are the periosteal node and diffuse osteitis.

**The Periosteal Nodes.**—Clinically this is the characteristic lesion. It takes the form of a localized, firm, painful, tender swelling most frequently seen on the subcutaneous border of the tibia, but fairly common also on the femur, humerus, and ulna. In congenital syphilis the tibia may present a marked forward curve, a condition known as "sabre-blade" tibia. Although the swelling is localized it is not sharply delimited, and gradually shades off on to the surrounding bone. The spirochetes appear to settle in the deeper vascular layer of the periosteum, and an abundant cellular granulation tissue is formed around the vessels not only in the periosteum but also in the mouths of the Haversian canals. The tension produced by this new tissue within the bony canals is responsible for the nocturnal boring pains alluded to by the Psalmist. The underlying bone is at first rarefied by the granulation tissue, but sclerosis rather than rarefaction is the characteristic lesion of syphilis, and in time the activity of the osteoblasts renders the bone denser than normal, and converts the granulation tissue on the surface into bone. Later in the disease there may be a gummatous periostitis, the center of the mass degenerating owing, in part at least, to the obliterating endarteritis which is so characteristic of luetic lesions. The gumma may ulcerate through the skin;



when the tough yellow slough comes away it exposes bare necrosed bone.

**Diffuse Osteitis**.—In this form, also called diffuse osteoperiostitis, the greater part of the shaft or the entire bone is involved from the periosteum to the medulla and from one articular cartilage to the other. The process is essentially the same as before, and a diffuse formation of granulation tissue with osteoporosis is followed by a sclerosing osteitis. New bone is laid down by the osteoblasts under the periosteum causing marked uniform thickening of the shaft, on the walls of the dilated Haversian canals causing greatly increased density of the bone, and in the medulla causing obliteration of that cavity. The entire bone is now dense and heavy. In the earlier stages the deep aching pains at night are likely to be especially severe. Gummatous osteitis may develop as in the periosteal form, but the gumma is less likely to ulcerate on the surface.

**Syphilitic Epiphysitis**.—This is so characteristic a feature of congenital syphilis in the new-born that a convenient method of diagnosing that condition at autopsy is to cut open the lower end of the femur or the upper end of the tibia and inspect the epiphyseal line. The normal line is thin as an edge of paper and pearly-gray, but in syphilitic epiphysitis it becomes broad, irregular, toothed, and of an opaque yellowish-white color. (Fig. 477.) When examined with a magnifying glass it has a granular appearance not unlike mortar. Microscopically it is seen that the process of ossification has become gravely disordered, irregular lines of cartilage extending into the diaphysis and thus causing marked widening of the epiphyseal line. In severe cases the place of the cartilage is taken by syphilitic granulation tissue, in which necrosis and caseation take place. It is evident that such a line, instead of uniting the epiphysis and diaphysis, merely forms a space which separates them, and the epiphysis may become detached either spontaneously or as the result of trauma, giving rise to syphilitic pseudoparalysis. The roentgen-ray appearance is diagnostic. Antisyphilitic treatment soon brings about reunion and normal ossification.



FIG. 477.—Syphilitic epiphysitis. The epiphyseal line of the lower end of the femur is broad and dark.

**Syphilitic Dactylitis**.—This is another manifestation of congenital syphilis in children. There is a diffuse infiltration of the marrow of one or more of the phalanges, with expansion and erosion of the medullary cavity and a formation of new periosteal bone on the surface. The affected digit presents a spindle-shaped swelling, which is easily mistaken for tuberculous dactylitis.

**Bones of the Face**.—Gummatous destruction of the bones of the nose and the hard palate are common in *congenital syphilis*. The bridge of the nose falls in at the root (saddle-nose), and there may be a large

perforation in the palate. The latter condition is also seen in the late stage of *acquired syphilis*.

**The Cranium.**—In the bones of the skull there may occur the two lesions already described, the periosteal node and diffuse osteitis. The *periosteal node* in congenital syphilis is usually multiple and symmetrical; the localized swellings affect principally the frontal and parietal bones and are grouped around the anterior fontanelle, giving an appearance of “bossing.” At first the new bone is spongy, but later it becomes sclerosed. In the acquired disease the periosteal node is rarely ossified. The granuloma remains soft and erodes the underlying bone, producing a worm-eaten appearance and sometimes complete perforation. If gummatous degeneration occurs there is likely to be a definite hole in the skull. *Diffuse osteitis* usually causes thickening and hardening of the cranial bones after a preliminary rarefaction. If gummatous formation and necrosis should occur, the surface of the skull may present an extraordinary worm-eaten and eroded appearance which is highly characteristic. Sequestra of varying size may be formed owing to interference with the blood supply of the bone.

**The Spine.**—Syphilis of the spine may take the form of a diffuse osteitis with marked thickening and hardening of several adjacent vertebræ. In other cases there is gummatous formation and breaking down, a condition apt to be mistaken for tuberculosis.

**Eosinophilic Granuloma.**—This is a painful inflammatory lesion usually of the skull, sometimes of a rib or long bone, occurring in children and young adults. It may be mistaken clinically for osteomyelitis, tuberculosis and Ewing's tumor. The lesion is soft, expands the bone, and consists of histiocytes, numerous eosinophilic polymorphonuclears, and sometimes giant cells arranged around cholesterol crystals. The etiology is unknown. The essential element in the lesion appears to be sheet-like collections of histiocytes. Farber suggests that the lesions are of the same basic character as those of Schüller-Christian's disease. In eosinophilic granuloma they are often confined to a single bone, and the distinctive feature is an intermingling of large numbers of eosinophils with the histiocytes, whereas in Schüller-Christian's disease the lesions are more widespread, and the histiocytes become loaded with lipid, so that the condition may be classified as a lipogranuloma. Letterer-Siwe's disease, in which the lesions are distributed throughout the skeleton and the soft parts, especially the lymph nodes, belongs to the same group.

## TUMORS OF BONE

In studying the difficult subject of bone tumors it is desirable to determine the constituents of the bone from which the various tumors arise. In many cases this is possible; in some it is difficult or impossible. Bone is a connective tissue which happens to be impregnated with lime salts. Anatomically it consists of periosteum, bone, and bone-marrow, while at each end of the growing bone there is epiphyseal cartilage. The periosteum consists of *fibrous tissue* and *osteoblasts*. The bone contains adult *bone cells* which are end-products incapable of proliferating and giving rise to a tumor, *osteoblasts*, and *osteoclasts*. The marrow consists of *marrow cells*, which need not be particularized further, and reticular or *reticulo-endothelial cells*. In general terms,

which will be subject to subsequent analysis, it may be said that the periosteal fibroblasts may give rise to fibrosarcoma, the osteoblasts to osteoma or osteogenic sarcoma, the osteoclasts to giant-cell tumor, the cartilage cells to chondroma and chondrosarcoma, the marrow cells to multiple myeloma, and the reticular or reticulo-endothelial cells possibly to Ewing's tumor. It is convenient to consider the innocent and malignant tumors separately.

In the introduction to their fine monograph on "Tumors of Bone," Geschickter and Copeland point out that it is not sufficient to consider the constituents of adult bone; the development of bone must also be taken into account. The development of the skeleton is never really complete, for transition forms between the different tissues persist in certain places at all ages, and may serve as the starting-point for tumors. Most primary bone tumors, they consider, arise in connection with such transitions in growth. In the lowest vertebrates the skeleton consists of connective tissue, higher in the scale cartilage takes the place of connective tissue, and finally the cartilage gives way to bone. This processional process is repeated in the human embryo, whose skeleton first consists of connective tissue, later of cartilage, and finally of bone. In the case of bones which are developed in membrane, *e. g.*, most of the bones of the skull, there is direct ossification in the primitive connective tissue, the connective-tissue cells becoming changed into osteoblasts which lay down bone. Such bones are not liable to the development of primary tumors. In the case of bones developed in cartilage the process is much more complex. The primitive connective tissue is first changed into fetal cartilage composed of small round cells; this develops into adult cartilage which becomes calcified; the calcified cartilage is removed by giant-cell osteoclasts, canalized and vascularized; finally permanent cancellous bone is laid down. This process goes on actively on both sides of the epiphyseal line, up to adult life on the shaft side, much later in life in the epiphyses. The embryonic connective tissue which has the ability to form both cartilage and bone persists in various places, and is especially abundant in the neighborhood of joints. If these facts be borne in mind, and if it be realized that developmental processes continue well into adult life, the skeletal and age distribution of tumors and the possible types which may occur will be better understood. Geschickter and Copeland use a histogenetic basis for their classification of bone tumors, somewhat in the same way as do Bailey and Cushing in their classification of the gliomas. "It is in delayed developmental steps in the persisting primitive connective tissue of the skeleton and in conjunction with subsequent histogenic steps, after the cartilage of the skeleton has been formed, that practically all primary bone tumors take origin."

**Innocent Tumors. — Osteoma.** — Most formations of new bone are not true tumors, but outgrowths from the surface known as *exostoses*; they are usually caused by the irritation of trauma. A *compact osteoma* is an ivory-hard tumor of the skull probably formed by the periosteal osteoblasts. A *cancellous osteoma* may be regarded as a bone in miniature, for it possesses its own epiphyseal cartilage by virtue of which it grows as long as the growth of the skeleton continues. It is therefore also known as an osteochondroma. Some writers call this tumor an *exostosis*. It arises from the end of one of the long bones, probably from a segment of epiphyseal cartilage, and the tumor is covered by a cap of cartilage until ossification is complete. As the bone grows in length, the tumor becomes displaced from the region of the epiphyseal line. An osteoma may grow from the bones of the face and attain a large size.

**Fibroma.**—Fibroma of bone is rare. It grows from the outer layer of the periosteum, usually in connection with the superior maxilla or the posterior wall of the nasopharynx where it forms a fibrous polypus.

**Chondroma.**—Cartilaginous tumors may arise from the epiphyseal cartilage or from the cartilage which precedes the developing bone, islands of which may remain unabsorbed. They occur during the growing period, and are commonest in the short bones of the hands and feet where they may be multiple. Single chondromas of large size may grow from the scapula, pelvis, neck of femur, and other bones. These single tumors often undergo myxomatous and cystic degeneration, and are then liable to show malignant change into a *chondrosarcoma*, especially when interfered with. It may be easier to detect this change from the clinical behavior and the gross appearance at operation (invasion, etc.) than from the microscopic structure. Invasion of the veins and metastases to the lungs confirm the malignant character of the change. A chondroma may grow on the surface or the interior of the bone. The latter form, known as an *enchondroma*, may cause expansion of the shaft, and when combined with cystic degeneration may give a roentgen-ray picture closely simulating that of giant-cell tumor. The condition known as multiple cartilaginous exostoses or chondrodysplasia is considered in connection with the bone dystrophies.

**Giant-cell Tumor.** This condition has in the past been called giant-cell sarcoma and myeloid sarcoma under the mistaken belief that the tumor was malignant. A more modern term is *osteoclastoma*, *i. e.*, a tumor of osteoclasts. It is locally destructive and may be invasive, but it does not give rise to metastases nor kill the patient, although it shows a fairly marked tendency to local recurrence. In actual practice it is well to associate the giant-cell tumor with the malignant tumors of bone, for it is from them that the differential diagnosis has to be made, although a central chondroma may sometimes give a similar roentgen-ray picture. In rare cases a giant-cell tumor may become malignant and metastasize to the lungs. When the benign tumor is removed by curettage a smooth-walled cavity should remain. If the tumor recurs there is danger of malignancy, and amputation should be considered.

The tumor develops in children and young adults, usually before the age of thirty years. It occurs principally at the ends of long bones, *i. e.*, in the metaphysis or the epiphysis (condyles of femur). The common location is the knee (lower end of femur, upper end of tibia), but it may occur in any bone developed in cartilage. The bones developed in membrane (cranium) are free. The reason for this will soon be apparent. The center of the bone is expanded, and the cortex often reduced to a mere shell, so that a spontaneous fracture may first attract the attention of the patient to the condition which is usually painless. Fairly thick bone trabeculae are left traversing the cystic lesion like beams supporting a crumbling building. This arrangement, best seen in the dried and macerated specimen from which

the soft tissue has been removed or in the operating room when the soft parts are curetted away, is responsible for the soap-bubble appearance (see below). The *roentgen-ray picture* is highly characteristic, and from it a diagnosis can usually readily be made. It shows a rarefied, multicystic, or trabeculated appearance as if the mass was composed of large bubbles, thinning of the cortex, and sharp limitation of the lesion from the surrounding bone and soft parts.

The *gross appearance* is that of a soft, dark red, hemorrhagic mass, sometimes with yellow areas. The material can be curetted away, and this is the usual form of treatment. Many cases respond well to radiation, but others do not. Cyst formation may occur in the center and the cyst may be filled with blood. There may be great expansion of the end of the bone. (Fig. 478.) *Microscopically* the tumor is composed of three types of cells: spindle-shaped cells, round cells, and giant cells. (Fig. 479.) The round cells are more numerous during the period of active growth. Predominance of the spindle cells indicates quiescence of the growth and a tendency to healing;

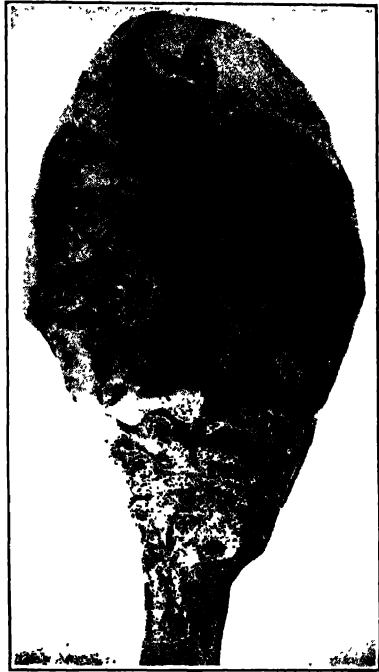


FIG. 478.—Giant-cell tumor of the upper end of the tibia. The material expanding the end of the bone is soft, red, and resembles blood clot.

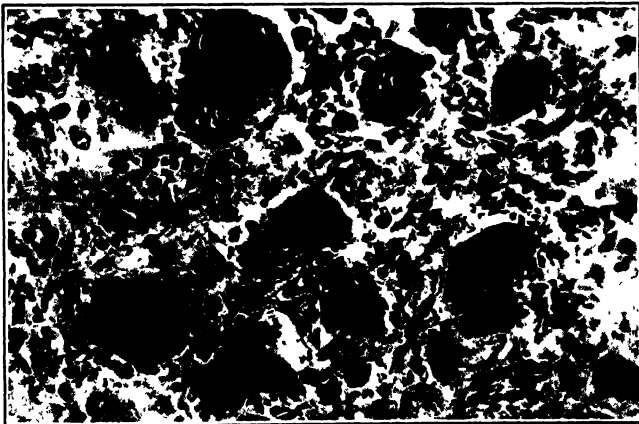


FIG. 479.—Giant-cell tumor of bone. The multinucleated giant cells are unusually numerous.  $\times 225$ ,

they are the cells which constitute the lesion in osteitis fibrosa. Giant-cell tumor of the vertebræ, which responds very favorably to even partial removal, is composed largely of spindle cells. The giant cells are large multinucleated cells of the osteoclast type. They may be numerous in one part, scanty in another. They differ from the rather similar cells of a granuloma in that the numerous small nuclei are situated toward the center of the cell and not around the periphery, and they are quite different from the tumor giant cells of an osteogenic sarcoma, which contain a few large irregular nuclei. The tumor is highly vascular, so that hemorrhage is frequent.

The *epulis* (*epoulis*, upon the gums) is a tumor in the gum growing in relation to the teeth. There are two forms: the giant-cell epulis, which is the common type and is similar in nature to the giant-cell tumor of bone, and the fibrous epulis which is similar in character to osteitis fibrosa. Epulides occur in children and young adults, and arise from the alveolar dental periosteum of the deciduous teeth (canine and bicuspid). They hardly ever occur at the site of the molars, which make only one (permanent) appearance. The growth is outward, often between the teeth, and does not invade the bone. In addition to the epulis, a central giant-cell tumor of bone may occur in the lower jaw between the symphysis and the mental foramen.

The nature of the giant-cell tumor has long been a matter of dispute. By some it is considered to be inflammatory rather than neoplastic in nature, the giant cells being regarded as foreign body giant cells. The most satisfactory way of regarding the lesion, as suggested by Geschickter and Copeland, is to consider giant-cell tumor and osteitis fibrosa as two phases of a transition process in the histogenesis of permanent bone; the former is an active vascularizing phase, the latter a healing phase. In the formation of normal bone there is a canalization, vascularization, and final removal of calcified cartilage, a process in which osteoclasts and round and spindle cells similar to those of the giant-cell tumor play an active part. This process may overstep the bounds of normal activity and become neoplastic, giving rise to a tumor which may be called an *osteoclastoma*. If the process is restrained and only slightly destructive, the result will be localized osteitis fibrosa with the possible formation of a bone cyst. Trauma is probably a factor of importance in disturbing the blood supply to the growing part, but the relation of trauma to a tumor must always be subjected to critical scrutiny.

This view throws light on a number of the features of giant-cell tumor. It explains its age incidence, its localization at the growing ends of bones (including the epiphysis), and its relation to osteitis fibrosa. The giant-cell epulis arises in a similar manner. The shedding of the deciduous teeth is brought about by the action of giant-cell odontoclasts, and the tumor is an *odontoclastoma*. The fibrous epulis corresponds to osteitis fibrosa. In the skull giant-cell tumors of central character, as distinguished from the epulides, are confined to parts developed in cartilage, *i. e.*, temporal fossa, the part of the

mandible between the symphysis and mental foramen which is developed from Meckel's cartilage, and the anterior part of the superior maxilla. The giant-cell tumors (xanthomas) of tendon sheaths may also be explained in this way. The calcified structures with the removal of which they are concerned are the sesamoid bones.

Stewart and others believe that the two processes are entirely distinct, and that the true osteoclastoma is a primary neoplasm unrelated to osteitis fibrosa. It is more sharply circumscribed than the giant-cell lesions of osteitis fibrosa and the rest of the skeleton is quite normal. The rare cases of malignant giant-cell tumor would rather support this view.

**Malignant Tumors.**—Malignant tumors of bone may be primary or secondary. Secondary tumors are carcinoma (including hypernephroma), and usually occur after middle-age. They are far commoner than primary tumors, and should always be suspected in a case of bone tumor in the latter half of life. Primary tumors are sarcomatous in type, and for the most part occur during adolescence. There are three principal types: *osteogenic sarcoma* (by far the commonest), *Ewing's tumor*, and *multiple myeloma*. To these must be added *chondrosarcoma*, as well as a number of rare types. The giant-cell tumor has to be compared with the primary malignant tumors for purposes of clinical differentiation. Osteogenic sarcoma and Ewing's tumor occur chiefly in childhood and adolescence, giant-cell tumors are commoner in the third decade, and multiple myeloma generally occurs after the age of forty years. The site of election of osteogenic sarcoma is at the end of the long bones (metaphysis), giant-cell tumor at the epiphysis, Ewing's tumor in the shaft of the long bones, and multiple myeloma in the flat bones.

**Osteogenic Sarcoma.**—This is the most common and the most malignant of bone tumors. It is a disease of the second and third decades (ten to thirty years), and is very rarely seen after the age of fifty years. It occurs at the end of the shaft (metaphysis) of the long bones, usually in the region of the knee (lower end of femur, upper end of tibia). Over 70 per cent of cases occur in the lower limb. The order of frequency is as follows: femur, tibia, humerus, pelvis, fibula. It hardly ever occurs in the forearm. A history of trauma is common but not so constant or convincing as in Ewing's tumor. Nothing is more difficult than to judge the relationship of trauma to tumor. There is no relation between fracture and any form of bone tumor. Martland has pointed out that osteogenic sarcoma may develop in those whose bones have become highly radio-active. In a group of girls who died from the ultimate effects of swallowing highly radio-active substances while painting the dials of luminous watches, 27 per cent of the deaths were due to osteogenic sarcoma. It was calculated that in the year 3491 A.D. the skeleton of one of these girls would still be giving off 185,000 alpha particles per second, each of these travelling at the rate of 18,000 miles per second.

The *gross appearance* depends on the stage. The first symptom is

pain, due to involvement of the sensitive periosteum, and this may precede the appearance of a tumor by weeks or months. When the tumor is well developed there is a fusiform mass at the end of the bone which fades away on to the shaft, giving a "leg of mutton" appearance. (Fig. 480.) At first the disease is confined to the bone, with involve-

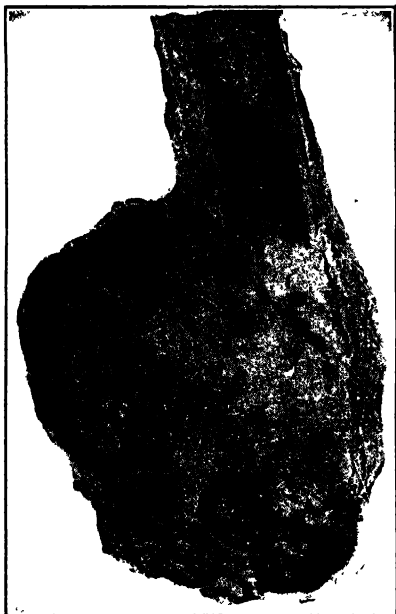


FIG. 480.—Osteogenic sarcoma of lower end of femur. The tumor has destroyed the shaft, and is both medullary and periosteal in distribution.

ment of the shaft, the medulla, and the periosteum, but in the later stages the periosteum is perforated with rapid dissemination of the grow thin the soft parts. There is a coincident absorption and deposition of bone; the original shaft is absorbed, but tumor bone is laid down in the subperiosteal space by the osteogenic tumor cells. It is curious to note that the innocent giant-cell tumor is destructive (osteolytic), while the very malignant osteogenic sarcoma forms new bone. This formation, however, is quite patchy, so that pathological fracture is likely to occur in the later stages. As the periosteum is lifted up from the bone by the tumor the vessels which enter the shaft from the periosteum are drawn out in parallel vertical lines, which form a scaffolding on which the new bone is laid down. Fine spicules are therefore found radiating outward from the central mass, and in the roentgen-

ray picture these give a very characteristic "sun-ray" effect. The consistence of the tumor varies with the amount of bone formed, which may be much or little. The tumor may be very soft and sarcomatous, or firm and fibrous, or hard and bony. The usual color is gray, but the tumor may be highly vascular and hemorrhagic, and may present cysts filled with blood. Necrosis and softening are common.

The *microscopic picture* is extraordinarily varied, so that different cases differ widely, and in a single case there may be the same pleomorphism as is seen in spongioblastoma multiforme of the brain. The *tumor cells* are osteoblasts, and three types may be seen. (Fig. 481.) (1) The most constant and characteristic form is a small spindle cell with hyperchromatic nucleus and poorly-defined cytoplasm. If the tissue is poorly fixed and stained, the cytoplasm may not be detected, so that the cells appear round, but an osteogenic sarcoma is never a round-cell tumor. (2) Other cells may be large and spindle-shaped or polyhedral. Mitoses are numerous in these cells. (3) Giant cells are



often present. These may be tumor cells or foreign body giant cells. The tumor giant cells may be mononuclear or may contain a small number of large nuclei. The cells have a more irregular, atypical, and neoplastic appearance than the foreign body giant cells. The latter are present when there is much bone destruction, and especially after an exploratory operation. The *intercellular substance* is as characteristic as the cells. It may be hyaline and fibrous, cartilaginous, myxomatous, osteoid, or osseous. Thus there may be formation of tumor bone. It is important for the pathologist to distinguish between tumor bone and true bone. Tumor bone is atypical and poorly formed, it blends with the stroma of the tumor, and it presents no bordering line of osteoblasts. When the stroma is largely fibrous, the sarcoma is of the sclerosing type. Calcium can be recognized by its dark blue color when stained with

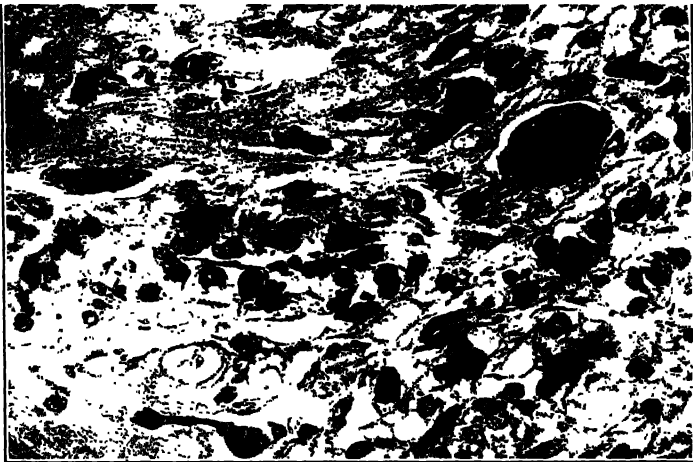


FIG. 481.—Osteogenic sarcoma showing the characteristically pleomorphic picture and a typical tumor giant cell.  $\times 300$ .

hematoxylin. If the bloodvessels are very abundant, the tumor is said to be of the telangiectatic type. Invasion of the thin-walled vessels is common, and tumor cells may form the actual walls of the blood sinuses. The limb must therefore be handled with great gentleness. It is easy for metastases to be set up at the time of operation. Preliminary radiation of the tumor, by closing the vessels, diminishes this danger to a considerable degree.

*Spread* takes place mainly by the blood stream, as is natural from the vascular arrangement just described. Metastases usually occur in the lungs, but if the tumor emboli pass the pulmonary capillaries they may lodge in other organs. It is important to note that secondary growths in other bones are very rare; multiple bone tumors suggest Ewing's tumor in the young and multiple myeloma in the middle-aged. The lymph nodes are sometimes involved, but any enlargement is

usually inflammatory. There is marked local invasion, and when the periosteum is perforated the tumor spreads rapidly through the soft parts and causes stretching of the skin. The *prognosis* is very bad, but not necessarily hopeless, especially if growth is first restrained by radiation. The younger the patient, the worse is the outlook.

The prognosis is bad, four-fifths of the cases being dead five years after amputation (Coley and Pool). This means, however, that 20 per cent are alive at the end of that time. Features which make for a good prognosis are age (best between twenty and forty years, bad in first decade, extremely bad in osteogenic sarcoma complicating Paget's disease), low-grade malignancy (histologic), and peripheral site of lesion.

**Ewing's Tumor.**—It was only in 1920 that Ewing separated this tumor from the general group of bone sarcomas under the heading of endothelial myeloma. It forms about from 10 to 15 per cent of all malignant bone tumors (including giant-cell tumors in the total). The *clinical history* is characteristic, but is quite suggestive of osteomyelitis, a disease for which this condition is very often mistaken both by the clinician and the pathologist. The patient is usually between the ages of five and fifteen years, and the disease is quite rare above thirty years. There is often a history of trauma, followed shortly by pain, at first intermittent but later continuous, fever, and the appearance of a swelling. When the swelling is incised a soft necrotic cellular material is obtained which is easily mistaken for pus. The occasional occurrence of a moderate leucocytosis still further adds to the difficulties of diagnosis. The *roentgen-ray picture* shows diffuse involvement of the greater part of the shaft. There is a combination of bone formation and bone destruction; formation in the early stage, destruction later. The new bone on the surface may present a laminated appearance like the layers of an onion. One of the most striking characteristics of the tumor is its *response to radiation*; it may melt away just like a lymphosarcoma, only to return again later. This characteristic is of great diagnostic value.

There can be little doubt that some of the cases described in the literature as Ewing's tumor are really examples of metastatic growths. In most of these cases the diagnosis is based merely on a biopsy or roentgen-ray report, whereas no case can be finally accepted without a complete autopsy examination. This truth is strikingly demonstrated by a case reported by Willis in his monograph on the "Spread of Tumors," in which a patient presented all the clinical, radiological and pathological (gross and microscopic) evidence of Ewing's tumor, and yet proved at autopsy to be a case of adrenal neuroblastoma with widespread metastases in the bones.

The *gross appearance* is that of a very soft disintegrating tumor resembling brain tissue. The bones most often involved are tibia, humerus, femur, fibula, clavicle, and os calcis in that order. The tumor probably (but not certainly) starts in the medullary cavity, from which it invades and widens the bone canals, expands the cortex,

and irritates the periosteum to lay down successive layers of new bone. This is normal bone laid down parallel to the surface, not tumor bone laid down at right angles to the surface as in osteogenic sarcoma. The bulk of the tumor is subperiosteal, the medullary cavity becoming narrowed or even occluded by new reactive bone. (Fig. 482.) Owing to the formation of new bone, pathological fracture is rare.

The *microscopic picture* is that of a round-cell sarcoma. The cells are round or polyhedral, very uniform in appearance, with a round nucleus and indistinctly defined cytoplasm which stains poorly. (Fig. 483.) They are closely packed together, and are arranged in sheets or columns, but may be grouped around blood spaces so as to give an angio-endotheliomatous appearance. There is no intercellular substance, in

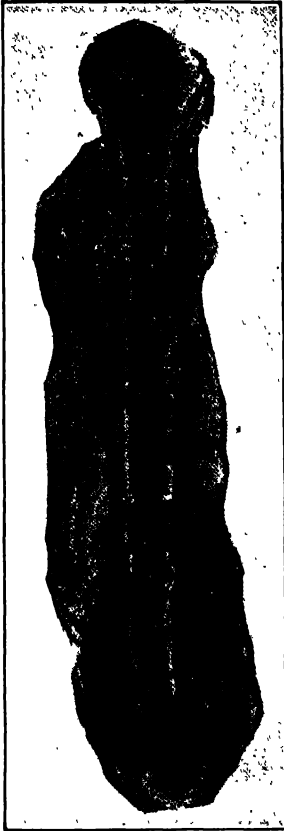


FIG. 482.—Ewing's tumor of humerus. The growth is characteristically diffuse, involving the entire shaft. There were secondary growths in several other bones. (From Boyd's Surgical Pathology.)



FIG. 483.—Ewing's tumor. Tumor cells are replacing the bone, fragments of which can be seen at left of picture.  $\times 600$ .

striking contrast to osteogenic sarcoma. The microscopic appearance gives little help in determining the *nature of the tumor*. Ewing originally called it an endothelial myeloma, in the belief from the occasional peritheliomatous arrangement that it arose from the perivascular endothelium. Other workers do not agree with this. As suggested

at the beginning of the section on Bone Tumors, it may be a reticulum-cell sarcoma arising from the reticulo-endothelium of the marrow. For the present it is best to use the non-committal name of Ewing's tumor.

*Spread* occurs within the shaft both longitudinally and transversely by means of the bone canals, which in decalcified sections are seen to be filled with tumor cells. Distant spread occurs to the lungs, lymph nodes, other organs, and other bones. The bone metastases are of the greatest importance in differential diagnosis. They are hardly ever seen in osteogenic sarcoma. In multiple myeloma there is usually multiple involvement of bones when the patient is first seen, but in Ewing's tumor the patient comes with a single tumor, the secondary growths not developing for several months. These growths are commonest in the skull, vertebræ, sternum, scapula, and ilium, *i. e.*, the flat bones containing red marrow. The *prognosis* is very bad, although the disease may sometimes be held in check for several years by means of radiation.

**Multiple Myeloma.**—This is a rare and highly malignant form of bone tumor. Perhaps it should be called a marrow tumor rather than a tumor of bone. The *clinical features* make the distinction from other bone tumors fairly easy. The age incidence is noteworthy, nearly all the cases occurring over the age of forty years. Pain is prominent at the beginning of the illness, but usually passes off, only to return later. The most striking feature is the multiplicity of the lesions, as indicated by the name. The flat bones containing red marrow are first involved, *i. e.*, sternum, ribs, vertebræ, skull, and pelvis; lesions may appear later in the long bones. In rare cases there may be a diffuse myelomatosis without the formation of definite tumor nodules. It is not possible to say with certainty if the lesions are primarily multiple or if one is primary and the others secondary. The condition is comparable with lymphatic leukemia, in which the bone-marrow throughout the body is involved. Indeed, Jackson and his associates consider that multiple myeloma should not be regarded as a bone tumor, but as a disease of the blood-forming organs like leukemia, for the lymph nodes as well as the marrow may be involved. This is best seen in the plasma cell type (plasma-cytoma), which may start in bone and spread later to lymph nodes, or starts in lymph nodes and spreads to bone; it may remain confined to the lymph nodes or be confined to bone. In rare cases the blood contains plasma cells. Jackson describes a case of plasmacytoma which commenced in the tonsil; this was removed, but the disease continued to spread through the lymph nodes, and after eight years caused generalized bone involvement. In less than 50 per cent of the cases there is Bence-Jones albumosuria; a protein appears as a cloud when the urine is heated to 55° C., disappears at 85° C., but reappears on cooling. Extract of bone-marrow has identical properties with Bence-Jones protein, and when this extract is injected into rabbits the protein appears in the urine. It is probably produced from leucocytes and

other marrow cells, thus explaining why it is sometimes found in leukemia. Renal insufficiency is common, especially in the advanced stages. Casts of Bence-Jones protein obstruct the tubules, which subsequently atrophy. Eventually there is marked atrophy of the

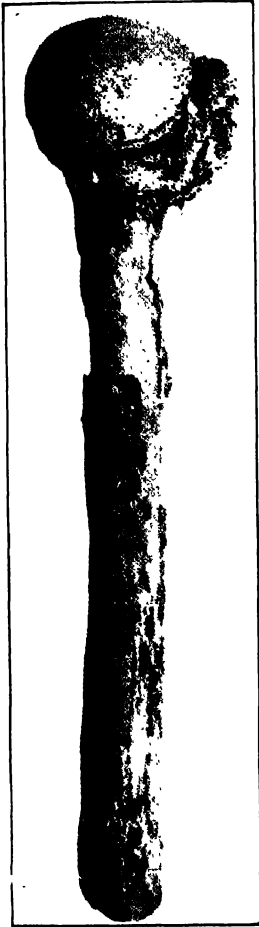


FIG. 484.—Multiple myeloma. Numerous punched-out cavities in the shaft of the humerus. (Kindness of Dr. H. M. Vango, from Boyd's Surgical Pathology.)

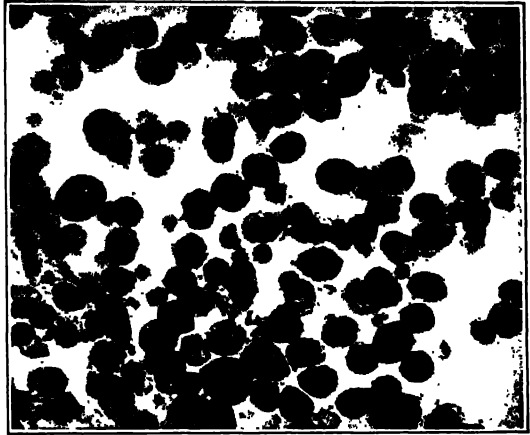


FIG. 485.—Plasma cell myeloma.  $\times 500$ .

cortex and renal failure. Hyperproteinemia occurs in many cases, with reversal of the normal albumin-globulin ratio, the albumin being low and the globulin high. There is a marked secondary anemia owing to replacement of the red marrow.

The *roentgen-ray picture* is very characteristic. The bone lesions are purely destructive and they are localized, so that radiologically they appear as round, punched-out, clear-cut areas in a number of bones. Owing to the rarefaction the cortex may be destroyed, so that pathological fractures are very common. The effect of radiation is similar to that in Ewing's tumor and lymphosarcoma. The lesions melt away marvellously, but soon reappear.

The *gross appearance* is that of soft gray tumors of the marrow, which are at first localized and produce marked destruction of the bone. (Fig. 484.) It is a pure rarefying lesion with no formation of new bone. Later the entire marrow cavity is filled with gray or red tumor tissue. *Microscopically* the picture resembles that of Ewing's tumor, but the cytology is not quite so uniform. The cells are round or polyhedral, are arranged diffusely, and there is no intercellular

substance. The predominant cell is a plasma cell (Fig. 485) with the addition of a certain number of lymphocytes, but sometimes the tumor is composed chiefly of the latter cells. The cell of origin is not known for certain, but it appears best for the present to regard multiple myeloma as a bone-marrow tumor.

*Spread* is principally to the other bones. Metastases to the internal organs, especially the liver and spleen, are not common. The spleen may be enlarged even without metastases. Curiously enough, metastases are almost never found in the lungs.

**Chondrosarcoma.**—This tumor usually arises as a malignant development of a chondroma. Invasion of the surrounding structures and of veins is often a better indication of malignancy than the microscopic appearance. Usually, however, the regular arrangement of cartilage cells is lost, and the growth is much softer and more cellular in character than the benign chondroma. Lung metastases are due to the frequent invasion of veins.

**Solitary Plasmacytoma.**—This is a rare tumor which may occur primarily in bone or in the upper air passages. As a rule, it is of only local malignancy, and is amenable to local removal or to operative treatment. In bones the plasmacytoma is usually multiple, and then constitutes one form of multiple myeloma.

**Periosteal Fibrosarcoma.**—This is a rare tumor arising from the outer fibrous layer of the periosteum and not involving the bone itself. It is a firm white mass consisting of spindle cells, and is less malignant than the osteogenic sarcoma. It is not a true bone tumor, and its relation to bone is quite fortuitous.

**Reticulum-cell Sarcoma.**—This rare bone tumor usually occurs before the age of forty, and often at a much younger age. It is apt to be mistaken for Ewing's tumor of one of the long bones. The cells are large, with abundant cytoplasm which may show pseudopodia. The nuclear outline is indented or kidney-shaped. With a silver stain a delicate reticulum is seen to encircle single cells.

**Liposarcoma.**—This tumor arises from the marrow, but involves the bone. It is a soft, yellow, slowly-growing tumor, composed of large cells arranged in alveolar groups with abundant cytoplasm filled with fine droplets of fat. On this account the tumor may be confused with secondary hypernephroma.

**Metastatic Tumors.**—Secondary tumors of bone are most likely to occur in carcinoma of the breast, prostate, kidney (hypernephroma), and lung, but many other malignant tumors may be the starting-point of secondary deposits. (Fig. 486.) Cancer of the thyroid gland deserves special mention. The bones commonly affected are the ribs, vertebræ, sternum, skull, and the upper end of the femur and humerus. In all of these bones the marrow is of the red variety and is well vascularized. In the shaft of a long bone the metastasis is often at the site of the nutrient artery. From all this it is evident that the usual mode of infection is by the blood stream, and not by lymphatic permeation as used to be thought. The deposit is formed in the medullary cavity. Roentgen-ray evidence goes to show that most of the tumors are purely osteolytic, the destruction not being associated with any bone formation. A round well-defined lesion is seen similar to that of multiple myeloma, although not quite so punched-out in character.

Hypernephroma affords a perfect example of an osteolytic process. Breast cancers are for the most part osteolytic, but a few are osteoblastic. Cancers of the prostate, on the other hand, are almost entirely osteoblastic, so that the lesions appear sclerotic in the roentgen-ray picture. A large amount of new bone is formed, which may obliterate the shaft and even form projections on the surface. Even here there is probably an associated osteolytic process, for fractures may occur. In the osteolytic form fractures are common, and may be the first sign of bone disease. It is rather remarkable that in spite of the destruction of bone, the fracture may heal satisfactorily. The blood picture may suggest a correct diagnosis. There is a leuco-erythroblastic anemia, with normoblasts and myeloblasts in the smear.

### THE OSTEODYSTROPHIES

There is a group of diseases of bone which is characterized by disorders of calcium metabolism and of ossification. Among these are osteitis fibrosa, osteitis deformans, osteomalacia, rickets, osteogenesis imperfecta, achondroplasia, hereditary chondrodysplasia, and marble bones may be mentioned. As they are disorders of the growth of bone they may be considered together under the heading of the osteodystrophies. It is becoming fashionable to consider many of these diseases as closely related to one another. Some writers, indeed, state that osteitis fibrosa (von Recklinghausen's disease), osteitis deformans (Paget's disease), and osteomalacia are one and the same condition; the difference depending on differences of age, vitality, etc. This view is strengthened by the similarity of the histological picture, which is one of rarefaction of osseous tissue and its replacement by young actively-growing fibrous tissue. Osteitis deformans is supposed to differ from osteitis fibrosa merely in that bone formation outstrips bone destruction. The fallacy in this argument is that rarefaction with fibrous tissue replacement is not a specific lesion, but is observed in a variety of bone diseases, just as perivascular collars of lymphocytes and plasma cells may be met with in the brain in such very different diseases as epidemic encephalitis, disseminated sclerosis, and syphilis of the nervous system. Further discussion along this line may be deferred until the various osteodystrophies are considered.



FIG. 486.—Secondary carcinoma of bone.  
× 250.

**Osteitis Fibrosa.**—This condition, also known as osteitis fibrosa cystica, may occur in a general or focal form. The two bear no relation to one another, although in both there may be the development of giant-cell tumors. The local form is confined to young people, whilst the general form may occur at any age. It is with the general form, sometimes called von Recklinghausen's disease of bone, that we are concerned at present. It is very much rarer than the focal variety.

**Clinical Features.**—The advanced clinical picture is easy to recognize, but the early stages may severely tax the diagnostic ability of the physician. The three principal symptoms are bone pains, tumor-like swellings and deformity of the bones, and spontaneous fractures. Of these, fracture is the most striking, and often is the first sign of bone disease. The fracture heals more readily than might be expected from the rarefied condition of the bone, but this may be explained by the fact that bone formation is also active. Owing to the softening of the bones they may become markedly bowed, and in severe cases the most extreme deformities may develop. The bones most often affected are the humerus, femur, and tibia, in that order. The disease is progressive and fatal. The roentgen-rays show widespread local rarefaction and sometimes cyst formation. The bones have a translucent and honeycombed appearance, the marrow is enlarged, the periosteum normal. The chemical changes in the blood, which are all-important, are described in the next section.



FIG. 487.—Osteitis fibrosa. The neck of the femur is converted into a large cystic cavity.

**Lesions.**—In advanced cases the highly porous bones may be much deformed and curved, they may be so soft that they can be cut with a knife, and the compact bone may be greatly thinned by the formation of cysts. (Fig. 487.) These, however, are not necessarily present, so that osteitis fibrosa is a more correct name than osteitis fibrosa cystica. The cysts may contain watery fluid or gelatinous masses. Abundant callus is found at the site of a recent fracture. The *microscopic appearance* is supposed to be specific, but a similar histological picture may be met with in other diseases, as pointed out above. There is resorption of bone with marked osteoporosis. (Fig. 488.) This goes hand in hand with vigorous new formation of young fibrous tissue which occupies the dilated Haversian canals and takes the place of



the absorbed bone. The marrow is also fibrosed. Some of this connective tissue may become converted into osteoid tissue, and formation of new bone can be detected with rows of osteoblasts, lining the spaces in the bone, but resorption always outstrips ossification and osteoclasts and giant cells form easily recognizable clumps. The formation of multiple giant-cell tumors or osteoclastomata is a characteristic feature of the disease. These may be minute or they may form quite large tumors which can be detected clinically. The new connective tissue is poorly vascularized, so that degeneration, softening, and cyst formation may occur. The lesions are at first in the form of circumscribed patches and are most marked at the ends of the growing bones, but in time they may fuse. The patient may die of osteogenic sarcoma, but this tendency is not nearly so marked as in Paget's disease.

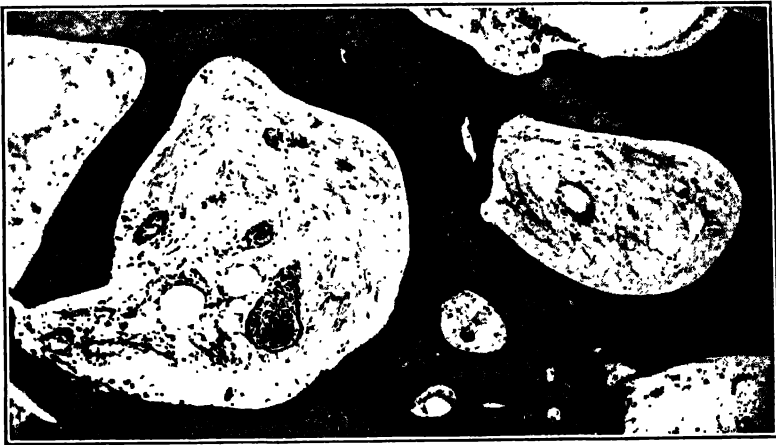


FIG. 488.—Osteitis fibrosa, showing the marked osteoporosis and absorption of bone  
× 50.

It was in 1901 that von Recklinghausen gave the first accurate account of osteitis fibrosa, and in 1904 Askanazy reported a case associated with a parathyroid tumor, but a quarter of a century elapsed before the significance of this association was recognized. The bone lesions are a manifestation of hyperparathyroidism, due usually to an adenoma but occasionally to hyperplasia of the parathyroids. The biochemical changes are similar to those produced by the administration of parathyroid extract, and the osteoporosis and other bone changes can be reproduced experimentally in animals by continued administration of the extract. The calcium removed from the bones appears in the blood, and the blood calcium rises from 10 mg. per 100 cc. to 15 or 20 mg. The phosphorus is below normal (3 mg. per 100 cc.), because the renal threshold for phosphorus is lowered by excess parathyroid hormone. Normally the calcium and phosphate

ions of the blood and the calcium phosphate of the bones are in a state of equilibrium and are subject to the law of ionic dissociation, *i. e.*, concentration of the ions, if altered, must vary inversely with each other, so that excess of calcium ions causes fall of phosphate ions. The low serum phosphorus is particularly valuable for differentiating hyperparathyroidism from such decalcifying diseases as widespread metastatic carcinoma of bone in which the blood may be flooded with calcium. Much valuable information regarding the chemical changes in the blood in this and other bone diseases will be found in Woodard's paper. In osteitis fibrosa the plasma phosphatase is considerably raised, although less so than in Paget's disease. There may be metastatic calcification of the arteries, and deposition of calcium in the renal pelvis with calculus formation. Large quantities of calcium are excreted in the urine, so that there is a negative calcium balance. The results of removing the parathyroid tumor may be among the most dramatic of postoperative phenomena; the blood calcium falls below normal so that there may be danger of tetany, the bone pains may be abolished immediately, the giant-cell tumors may diminish in size in the course of a few weeks, the renal calculi may break into fragments which are passed into the bladder, there is a marked gain in weight, and cripples may throw away their crutches.

**Focal Form of Osteitis Fibrosa.**—This is very much commoner than the generalized form. It bears no relation to that condition, for it is unconnected with hyperparathyroidism and the blood calcium and plasma phosphatase are normal. It occurs at the end of one or more of the long bones during their period of growth and is often first discovered through a spontaneous fracture. Cyst formation is common, as is the formation of a giant-cell tumor. It is probably a perversion of the normal process of removal of calcified cartilage by vascular connective tissue preparatory to the formation of true bone. This matter has been discussed in connection with giant-cell tumor of bone.

**Paget's Disease.**—This condition, also known as *osteitis deformans* (although not nearly so deforming as von Recklinghausen's disease), was first described by Sir James Paget in 1876. It is usually regarded as a rarity, but Schmorl, examining the entire skeleton in his autopsies, collected 138 cases in the course of five years. There is first softening and later overgrowth of bone; during the period of softening characteristic deformities develop. A number of bones are usually affected, but the disease may remain confined to one bone for many years. The former or polyostotic variety is common, but the latter or monostotic form is relatively rare, often remaining subclinical. The monostotic form is commonest in the tibia, the polyostotic is most frequent in the sacrum and vertebræ. It is not certain if they are variations of the same disease.

**Clinical Features.**—The disease usually begins over the age of forty. It may be familial. I know of two families in each of which three cases occurred. The legs are generally first affected, but the earliest change may be in the skull.

The softened bones are bent, the femur outward, the tibia forward. They become hardened again in this position and look as if they had been bent by the hands of a giant. Persistent bone pains in the legs may appear before the deformity. The head enlarges, and the patient presents himself with a history that he has to buy hats of ever-increasing size. The head comes to present a very characteristic appearance, for it is a triangle with the base above, the face escaping almost completely. Occasionally the bones of the face are greatly thickened (*leontiasis ossea*). A kyphosis or posterior curvature of the softened spine is very common and reduces the height of the patient. The general appearance in the advanced stage of Paget's disease is highly characteristic. The short squat figure with bent shoulders, curved back, sunken chest, and great head hanging forward, as it waddles along with bowed legs, out-turned toes, and the aid of a stick, is a living justification for the name *osteitis deformans*. The roentgen-ray picture is characteristic even before any deformity has appeared. The affected bones are thick and dense, although the medullary cavity is widened, and the vault of the skull presents a peculiar serrated (cock's comb) appearance which is pathognomonic. The disease is progressive, but, unlike *osteitis fibrosa*, does not usually shorten life. There is, however, a fairly strong tendency to the development of osteogenic sarcoma. When that tumor occurs over the age of fifty years it is almost always associated with Paget's disease. Arteriosclerosis is often very marked. The blood phosphatase is very high, and may be over 100 units.



FIG. 489.—Paget's disease of the skull; great thickening of the bone and cyst formation.

**Lesions.**—The bones commonly affected are the skull, vertebrae, and bones of the leg. In Schmorl's material the spine (including the sacrum) was most frequently involved. At first the bones are soft and easily cut with a knife; it is at this stage that the deformities occur. Later the bone becomes hard and of increased thickness. There is a thick deposit of subperiosteal bone on the long bones and on the skull, and the surface is rough and irregular. In spite of the thickening the new bone is of a porous character, as can be demonstrated by pouring water into the thick skull cap through which it runs as through a sieve. The thick, hard, curved bones are very characteristic of Paget's disease. The thickening is most strikingly seen on the cut surface of the skull cap, and a pathological diagnosis can readily be made from it alone. (Fig. 489.) *Microscopically* there is first a replacement of the

original bone by connective tissue, and then a substitution of finely-porous cancellous bone which gradually becomes harder. Absorption and apposition go on together, but the latter outstrips the former so that the bone becomes thick though still finely porous. One of the most characteristic features of the microscopic picture is the great number and *irregular* arrangement of the lamellar systems, which is seen in no other disease of bone. This gives what is known as a *mosaic* structure (Fig. 490), due to variously shaped areas of new and old bone fitted together like pieces in a jig-saw puzzle. These pieces are not arranged around vascular canals to form Haversian systems; there



FIG. 490.—Paget's disease of bone showing mosaic appearance.  $\times 200$ .

is no formation of an "osteon." The cement lines are wide, prominent and irregularly scalloped. Cyst formation is very rare, and so is the formation of giant-cell tumors. The medullary cavity is filled with fibrous tissue. In about 10 per cent of cases sarcoma develops and kills the patient. This may be fibrosarcoma or osteogenic sarcoma. Fibrosarcoma, which is the commoner, arises from the new cellular connective tissue. The osteogenic sarcoma is not identical with the classic form, and may show great numbers of tumor giant cells. There are often multiple foci of sarcoma in different bones.

The *nature of the condition* is uncertain. By some it is believed to be a variation of osteitis fibrosa occurring at a later age, but the blood calcium and phosphorus are normal, and there is no parathyroid hyperplasia. Edholm,

Howarth and McMichael have demonstrated that in generalized Paget's disease the bone blood flow is greatly increased, sometimes up to twenty times the normal. This produces the same effect on the general circulation as do free arteriovenous communications, with resulting congestive heart failure. This effect is not seen in the localized form. It is of interest to note that Paget considered the bones to be hyperemic, and in one of his original cases the heart was dilated at autopsy. Other guesses have been made, but they are too baseless to be mentioned.

**Osteomalacia.**—This is a very rare disease in North America, although fairly common on the Continent. It is considered in this place because for

years it has been confused with osteitis fibrosa, but it is much more closely related to rickets. Osteitis fibrosa is an endocrine disorder; osteomalacia and rickets are deficiency diseases, the former affecting the adult, the latter the child. In all three the bones are poorly calcified, but in osteitis fibrosa the calcium is removed from the bones on account of parathyroid activity, while in osteomalacia and rickets calcium is not laid down in the bones because of lack of vitamin D, the other great regulator of calcium metabolism. Osteomalacia often comes on during pregnancy, owing to the great drain on the calcium of the woman's bones which occurs at that period. Starvation may be a factor, and this probably accounts for the increase of the disease among the Central Powers during the war of 1914-1918. The disease is one of middle life, and is almost confined to women who are pregnant or exhausted by much child-bearing. The bones commonly affected are the lumbar vertebræ, pelvis, and the bones of the legs. Osteomalacia provides a good example of the difficulty of drawing correct conclusions regarding the osteodystrophies. The parathyroids may be enlarged, but it is almost certain that the hyperplasia is secondary and not primary, an attempt to offset the deficient calcification of the bones. The same secondary parathyroid hyperplasia is seen in rickets.

As the name implies, the bones are softened owing to loss of calcium, so that they can be readily bent or cut. In the roentgen-ray picture they present a faint and lace-like appearance. The vertebræ are compressed, so that the patient becomes shorter. Owing to softening of the pelvis the promontory of the sacrum is pushed forward and the acetabula are pushed inward, so that the pelvic inlet is distorted and narrowed, making normal delivery impossible. The bones of the leg are markedly bowed. Microscopically the normal bone is replaced by newly-formed bone which is calcium-free, *i. e.*, it remains as osteoid tissue. As Pick remarks, osteomalacia from the morphological standpoint is rickets in adult life, but the lesions are not most marked at the growing ends of the bone as in rickets, for growth of bone has now ceased.

**Senile Osteoporosis.**—In the later period of life, particularly in women after the menopause, the bones tend to become rarefied. Bone absorption may be particularly marked in the vertebral column. The condition is due to a defect in the reparative mechanism of bone, the probable basis of which is the endocrine imbalance of later life, especially in the female (Albright). The notable feature of the blood chemistry is the lack of any abnormal findings. The absence of an elevation in the serum alkaline phosphatase serves to distinguish this condition from osteomalacia and from many metastatic tumors of bone (Woodard).

**Osteogenesis Imperfecta.**—This rare condition, also known as *fragilitas ossium*, is an affection of childhood in which the bones are imperfectly ossified. There is a marked hereditary and familial tendency. The child may be born dead with multiple fractures acquired *in utero*, it may be born alive and die afterwards from many fractures produced during delivery, or it may be born apparently healthy and only show evidence of brittleness during childhood and adolescence. There is a tendency for the condition gradually to disappear. A remarkable feature of the disease is that many of the patients have blue sclerotics; the color is due to partial visibility of the choroid through the sclerotic owing to some defect in that coat. Blue sclerotics may be associated with brittle bones in one member of the family, while the others have blue sclerotics but no special tendency to fractures. Otosclerosis may develop after the age of twenty years. The blood calcium and phosphorus are normal. The parathyroid glands may be enlarged. In one very severe case in a still-born baby which I examined the enlargement was very noticeable. In addition to the fractures there may be bony swellings, especially in the temporal region so that the ears are turned out and down, and sometimes in the frontal or occipital regions. The ossification of the skull may be so incomplete that it is a mere membranous bag or a few bony plates; if ossification has proceeded further, the skull may present a large number of Wormian bones. The teeth

are poorly calcified and may be translucent. The bones are very light and fragile. Microscopically the trabeculae are narrow and widely separated. Few osteoblasts can be seen, and it is possible that there may be a deficiency of phosphatase production.

**Achondroplasia.**—This is another rare defect in ossification, confined to bones ossified in cartilage, *i. e.*, long bones and base of skull; the rest of the skull and the bones of the face develop normally. The child may die shortly after birth or may grow up as a stunted dwarf with short arms and legs, normal trunk, large head, depressed bridge of nose, and squat hands with fingers of equal length (trident hand). (Fig. 491.) The shortness of the bones is due to failure of the epiphyseal cartilage to function. The epiphyses are enlarged and with the short diaphysis give the bone the appearance of a collar stud. The indrawing of the nose is due to relative shortening of the base of the skull from imperfect ossification. Microscopically the cells of the epiphyseal cartilage are large, are not arranged in rows, and show an undisciplined tendency to grow in all directions; there is no evidence of active ossification. The disease, which is often familial, is probably due to some endocrine disorder. Dachshunds are achondroplastic dogs selectively bred.



FIG. 491. — Achondroplastic dwarf.

**Hereditary Chondrodysplasia.**—This rare condition is also known as *multiple cartilaginous exostoses*. It appears to be a hereditary disturbance of the metabolism of cartilage and bone. It begins early in life and is commoner in boys than girls. Only the bones ossified in cartilage are affected, flat bones as well as long bones. The two chief changes are deformities from retardation of growth and multiple exostoses. The growth retardation may affect any bone developed in cartilage and sometimes only one part of a bone, *e. g.*, acromion process of scapula. The radius or tibia may not grow properly while the ulna or fibula does, with resulting bowing of the bones. The radius becomes a bent bow; the ulna serves as its tight string.

The exostoses appear on the shaft of the bones, often as the result of injury to the periosteum. At first they consist of cartilage, but later they may be completely ossified. There may be great numbers of these exostoses. Swellings may develop in the region of the epiphyseal lines, causing enlargement of the ends of the bones. The disease ceases when skeletal development is complete. Nothing is known as to the cause of the condition.

**Marble Bones.**—This extremely rare condition is also known as Albers-Schönberg's disease. A better name is *osteopetrosis*. The disease shows a strong familial tendency. It is characterized by excessive calcification of osteoid tissue and absence of true ossification as shown by lack of bone lamellae and of osteoblasts. The bones therefore lose their elasticity and fractures are common. The condition occurs in childhood or can be traced back to that period. In the roentgen-ray picture the normal structure of bone is replaced by a homogeneous, intensely dense, marble-like appearance. The principal features may be catalogued as follows: All the bones are very dense, particularly the ends of the long bones; narrowing of the cranial foramina causes optic atrophy and other cranial nerve disturbances; narrowing of the medullary cavity leads to osteosclerotic anemia; hydrocephalus, interference with dentition, and enlargement of the liver and spleen may be present. The cause of

the condition is unknown, but some suggestive work of Selye's may be noted. He found that when small doses of parathyroid extract (parathormone) are given to the experimental animal over long periods of time, instead of rarefaction there is apposition, *i. e.*, increased bone formation, owing to stimulation of the osteoblasts. The bones assumed the same extremely dense character as is seen in marble bones.

**Hypertrophic Pulmonary Osteo-arthritis.**—This condition, also known as *Marie's disease*, is largely due to deficient oxygenation of the tissues, especially when associated with the absorption of toxins. It is met with, therefore, in such pulmonary conditions as bronchiectasis, chronic phthisis, empyema, and in congenital heart disease. There is a subperiosteal formation of new bone with thickening of the bones of the hands and feet, and a lesser involvement of the long bones. The corresponding joints may show swelling and thickening of the synovial membrane. *Clubbing* of distal phalanges (fingers and toes) may be part of osteo-arthritis or may occur apart from that condition, especially in subacute bacterial endocarditis. The clubbing is largely due to thickening of the soft tissues, probably from edema due to deficient oxygenation. The nails are thickened and characteristically curved, with or without an accompanying thickening of the phalanges.

**Fibrous Dysplasia of Bone.**—Attention has been drawn by Lichtenstein and Jaffe to a condition which may readily be confused with osteitis fibrosa cystica. It appears to be a congenital anomaly in development resulting in tumor-like malformation of bone, and has been appropriately named fibrous dysplasia. One or several bones may be involved. Where the condition is multiple the lesions have a tendency to be unilateral. Many cases are asymptomatic, but pathological fracture may occur. Almost any bone may be involved. I have seen one case in which two adjoining ribs presented huge swellings mistaken for giant-cell tumor, and another in which there was cyst formation in the skull. In the severe forms, usually occurring in childhood, there may be extraskeletal anomalies such as pigmentation of the skin, premature sex development in females, premature growth, and hyperthyroidism. These are known collectively as Albright's syndrome.

The affected part of the bone is expanded and the cortex is thinned, the interior being filled with rubbery, sometimes gritty, fibrous connective tissue. The microscopic appearance of the connective tissue varies; in some places it may be cellular, with spindly cells arranged loosely in whorls, whilst elsewhere it may be densely collagenous. New trabeculae of bone may be formed through metaplasia of the connective tissue, thus accounting for the grittiness referred to above. In addition there may be small cysts, occasional hemorrhage, and giant cells. In the x-ray film there is a localized rarefaction which is readily mistaken for cyst formation.

**Hyperostosis Frontalis Interna.**—This obscure condition, also known as metabolic cranio-pathy, is characterized by a peculiar bossy thickening of the inner table of the frontal bone associated with metabolic and psychotic disturbances. The cranial capacity is decreased, with resulting atrophy of the frontal lobes. The radiological appearance is readily recognized. The metabolic changes are those of pituitary dysfunction, particularly obesity, virilism and menstrual disorders, and may precede the bony changes. The condition is usually found in women past the menopause. There may be no metabolic or psychotic symptoms, and the bony lesions may be discovered by chance at autopsy. The etiology is unknown.

**Rickets.**—Rickets is a deficiency disease in which an osteodystrophy is responsible for some of the main clinical symptoms, but its effects are by no means confined to the skeleton. It is a fascinating disease to study because of the remarkable advances in knowledge which have been made in recent years owing to the combined efforts of the biochemist, the experimental pathologist, the radiologist, and the clinician.

**Etiology.**—Rickets is a deficiency disease in which the inorganic constituents of bone, calcium and phosphorus are not properly utilized. Deficiency of four factors has to be considered: calcium, phosphorus, vitamin D, and light. Phosphorus deficiency is more serious than calcium deficiency. Vitamin D facilitates the absorption of calcium and phosphate from the intestine. Light, or rather the short wave ultra-violet rays, activates the sterols in the skin and converts them into vitamin D.

These four deficiency factors must be considered collectively, for they often act together. Thus an amount of calcium in the diet sufficient to prevent rickets becomes insufficient when the phosphorus is also lowered, even though only to a moderate degree. The two seem

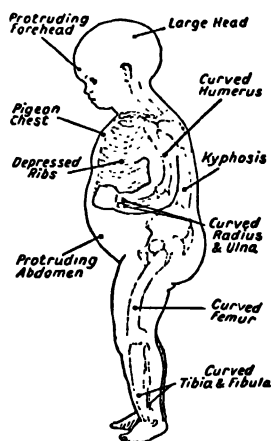


FIG. 492.—Clinical features of severe rickets. (Harris, *Vitamins in Theory and Practice*, courtesy of Cambridge University Press.)

to work hand in hand. The same is true of the action of light. When rats are fed on a rickets-producing diet they can be protected by being rayed for two minutes each day with the mercury-vapor-quartz lamp. In actual practice rickets is a disease of the slums of large cities especially in countries which get little sunshine. Here all four factors are at work: the food is deficient in quality as well as quantity (calcium, phosphorus, and vitamin D) and there is a deficiency of ultra-violet light. The fault lies in the quality rather than the quantity of the food. A child may be starved and emaciated, yet show no sign of rickets, while a plump baby may be markedly rachitic. A diet almost exclusively of carbohydrates or proteins will produce rickets, but the addition of cod-liver oil will cure the disease. If the child gets a proper diet and sufficient sunlight, cod-liver oil is never

necessary. Rickets is a disease of bottle-fed babies, except in the case of negro children whose dark skin prevents the light from activating the ergosterol.

**Clinical Features.**—Rickets is a disease of infancy and early childhood covering the period from six months to two years, but the bony changes then instituted may persist for the rest of the patient's life. It is a disorder of calcium and phosphorus metabolism, and examination of the blood shows that either there is a low serum calcium with a rather low inorganic phosphate or normal calcium with very low phosphate. Among the constitutional symptoms are anemia, enlargement of the spleen and lymphoid tissue, flabbiness of the muscles, sweating, and poor formation of the teeth. The bony changes are the combined result of defective calcification and excessive proliferation of epiphyseal cartilage. (Fig. 492.) The bones are soft, so that the femur bends outward, the tibia forward, and the spine backward (kyphosis) or laterally (scoliosis). The constant pull of the tendo Achillis on the foot in the sitting position may produce a curved sabre-shaped tibia. In the softened pelvis the promontory of the sacrum is pushed forward and the acetabula



inward, giving the same narrowed pelvic inlet as is seen in osteomalacia and constituting an insuperable obstacle to normal delivery in later life. The sternum is pushed forward (pigeon breast), leaving a vertical groove on each side of the thorax. The epiphyseal proliferation gives rise to a series of nodules at the costo-chondral junctions (the rickety rosary), and to nodular swellings at the wrists, knees, and ankles. Bones developed in membrane also suffer, and there is heaping up of spongy bone (bossing) in the frontal and parietal regions so that the skull becomes box-like. There may be a thinning of the back of the skull where the head rests on the pillow, a condition known as craniotabes. This is due to absorption of the non-calcified osteoid tissue from pressure. In the roentgen-ray picture the normal thin epiphyseal line is broad and irregular; periodic examination of this line forms a convenient method of estimating the effects of treatment, and has been much used in experimental work.

**Lesions.**—The essential rachitic lesion is an abundant formation of osteoid tissue which fails to become calcified. The bones are therefore soft and the epiphyses can be cut with a knife. The degree of involvement of the ends of the long bones is proportionate to the rapidity of growth of the epiphyseal cartilage. The most rapid growth occurs at the junction of the ribs and costal cartilages, the lower end of the femur, and the upper end of the humerus in that order. The widening of the epiphyseal line can be seen with the naked eye; it may be 10 or 15 mm. in diameter and is markedly irregular. It is widened not only in depth but also laterally, thus accounting for the nodular swellings of the ribs and at the ends of the long bones.

The *microscopic picture* is one of osteoid tissue formation without calcification. Normal epiphyseal cartilage is a narrow plate covered by bone on the epiphyseal side and penetrated by vessels on the diaphyseal side. There is continuous proliferation of cartilage cells on the epiphyseal side and simultaneous degeneration of matured cells on the diaphyseal side with the formation of cavities. These are entered by capillaries accompanied by osteoblasts which deposit osteoid on the exposed cartilaginous matrix. Thus there is a constant increase of cells on one side of the disc and disappearance of cells on the other side. The degenerated cells are clear and empty. The first microscopic sign of rickets is absence of the layer of clear cells and thus absence of ingrowth and capillaries. The matrix between the non-degenerated cartilage cells does not become calcified. The severity of the rickets is indicated by the volume of cartilage and the amount of osteoid. The essence of the condition is a retardation of the two normal processes of the cartilage sequence and calcification of the matrices. The cartilage cells are not arranged in rows as in normal growing bone, and the zone of proliferating cartilage may be ten times as deep as normal, sending out prolongations into the metaphysis which give the line the irregularity so characteristic of the gross appearance. (Fig. 493.) The zone of preparatory calcification is almost completely free of calcium. Beyond this there is a broad zone of osteoid tissue containing trabeculae and resembling bone morphologically, but without the all-important lime salts. The osteoid tissue extends out to the perichondrium, where it causes the characteristic

thickenings observed clinically. The bosses on the skull and the new periosteal and endosteal bone are also composed of this same material. When healing occurs there is active calcification of the osteoid tissue so that dense bone is formed. In course of time much of this new bone (rickety rosary, etc.) disappears.



FIG. 493.—Rickets. There is extreme widening of the epiphyseal line and thickening of the bone in this region. There is complete absence of calcification of the osteoid tissue.  $\times 7$ .

**Scurvy-rickets.**—This condition, also known as *infantile scurvy* and *Barlow's disease*, is a form of scurvy and bears no relation to rickets. It is characterized by subperiosteal hemorrhages, and is considered in connection with vitamin C deficiency in Chapter XI.

**Renal Rickets.**—This condition has already been described in Chapter XXIV. In children suffering from chronic renal insufficiency the bones may develop lesions similar to those of rickets. Osteoid tissue is formed in excess but not calcified, so that deformities occur. The relationship between the bone and renal lesions is not at present understood, but the disturbance of growth is supposed to be connected with the marked retention of phosphorus which constitutes the most striking of the biochemical changes. As the concentration of ions varies inversely, the calcium falls as the phosphate rises, and this leads to drainage of calcium from the bones. In some cases it is possible that the primary defect may be in the parathyroids, the changes in the kidneys being secondary.

**Cœliac Rickets.**—In cœliac disease, characterized by the passage of voluminous fatty stools in young children, there is frequently marked osteoporosis with a tendency to spontaneous fracture, and occasionally there is typical evidence of rickets at the epiphyses. In this case the etiological factor is faulty absorption of calcium in the intestine.

**Bone Changes in Gaucher's Disease.**—In Gaucher's disease, the bones may occasionally show marked changes (Pick). The marrow cavity is infiltrated with large lipoid-filled Gaucher cells. Owing to a similar infiltration the cortex may appear to be coarsely vacuolated or may be greatly thinned, so that spontaneous fractures occur. The vertebræ suffer severely; their bodies may be crushed, with resulting shortening of the body length and the produc-

tion of spinal deformities. In the roentgen-ray picture, in addition to general decalcification, there are large defects in the bone and thinning of the cortex.

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## CHAPTER XXXIII

### THE JOINTS

**Descriptive Outline.**—In describing disease in a joint the following structures should be considered: synovial membrane, contents of synovial cavity, articular cartilage and underlying bone, joint capsule and ligaments, periarticular tissues, overlying skin. The synovial membrane is thin, but it may be greatly thickened in disease. Its surface and that of the articular cartilage is smooth and glistening. The synovial cavity, which is merely a potential one, contains only a few drops or rather a film of fluid.

#### ACUTE ARTHRITIS

Acute inflammation of a joint is caused either by bacterial infection or by trauma, such as a blow or sprain. *Trauma* gives rise to a mild though acute inflammation. The joint is swollen, the swelling being due partly to an increase of synovial fluid which may become cloudy or blood-stained, partly to inflammatory swelling of the synovial membrane which is congested and infiltrated with leucocytes. The *bacterial infections* may be suppurative or non-suppurative.

**Suppurative Arthritis.**—The common infecting organisms are staphylococci and streptococci. The suppuration may be part of a pyemia in septicemic conditions such as ulcerative endocarditis or puerperal sepsis, or no other focus may be found. The infection may spread from the bone as in acute osteomyelitis, or may be introduced from without by a perforating wound of the joint. In pyogenic infections such as pneumonia and meningococcal meningitis there may be suppuration of one or more joints. An acute arthritis, usually non-suppurative in character and resembling that of rheumatic fever, may complicate scarlet fever, and inflammatory joint lesions may occasionally develop in the course of typhoid, dysentery, and other acute fevers.

In suppurative arthritis the *synovial membrane* is hyperemic, swollen, soft, and infiltrated with pus cells. The cells lining the surface are cast off, and fibrin is deposited on the raw surface. The *synovial fluid* is milky or frankly purulent, crowded with polymorphonuclear leucocytes, and usually contains the infecting organisms. The *articular cartilage* becomes eroded and the underlying bone is exposed, causing great pain when the joint is moved. The *ligaments* are softened and give way, so that the joint becomes completely disorganized and is often dislocated. The *capsule* may then rupture, the pus making its way into the periarticular tissues. This is a picture of the most severe form of suppurative arthritis. In other cases the infection is milder and may be localized to the synovial membrane (*acute synovitis*), with little or no destruction of the joint. When there has been destruction

of tissue there will be fibrous union (ankylosis), and if the articular surfaces are destroyed the union may be cartilaginous or bony.

**Non-suppurative Arthritis.**—Most examples of acute arthritis are non-suppurative, the inflammation is confined to the synovial membrane (acute synovitis), there is no destruction of tissue and therefore no permanent stiffness. *Traumatic synovitis* due to a strain is a good example of the condition. The synovial membrane is swollen, juicy, and congested, and infiltrated with inflammatory cells, while the synovial fluid is increased in amount, cloudy, and contains desquamated endothelium and small numbers of leucocytes. *Rheumatic arthritis* is the acute non-suppurative arthritis of rheumatic fever. Several joints are affected one after the other. There is an acute synovitis with excess of turbid fluid in the joint. Extreme tenderness is characteristic of the swollen and acutely inflamed joint. There is some involvement of the subsynovial and periarticular tissue and ligaments, and rheumatic nodules similar in structure to the Aschoff bodies in the heart may be present in the subcutaneous tissues. The inflammation usually undergoes complete resolution, but if there is severe involvement of the periarticular tissue, some permanent stiffness may result. The possible relationship of acute rheumatic arthritis to rheumatoid arthritis is discussed in the next section.

### CHRONIC ARTHRITIS

The term chronic arthritis has come to be used in a special sense. It does not mean, as the name suggests, a chronic inflammation of the joint, but a slow, progressive, crippling disease. It is not generally realized that this is the greatest single cause of prolonged disability in the world today. Thus in Sweden 9 per cent of all cases of permanent pensionable invalidity are due to arthritis, while in the state of Massachusetts the cases of disability number 140,000, compared with 25,000 from tuberculosis. The Metropolitan Life Insurance Company of New York estimates that the disease is responsible for an annual loss of 7,500,000 weeks of work and costs \$200,000,000. The English figures are very similar. The cases can be divided into two great groups which appear to constitute quite separate entities, although confusing intermediate and mixed forms are encountered. These groups are *chronic infective arthritis* and *chronic degenerative arthritis*. The former is commonly called rheumatoid arthritis, the latter osteoarthritis. They are sometimes included under the common heading of *arthritis deformans*, a name only too well justified.

**Rheumatoid Arthritis.**—This form is also called *chronic infective arthritis*, an excellent term which separates it sharply from osteoarthritis. It commonly occurs in women of between twenty and forty years, *i. e.*, during the period of reproductive activity. The onset is gradual and insidious, but in children it may be quite acute, with multiple arthritis, fever, leucocytosis and enlargement of the spleen and lymph nodes, a condition known as Still's disease. Even in adults

the onset is sometimes fairly sudden. The small joints of the hands and feet are the chief sufferers, but the larger joints may be involved later, the hip usually escaping. The course of the disease is marked by remissions and exacerbations, and at any time it may be arrested, but the injury to the joint is permanent, and the hands and feet are twisted, gnarled, and crippled for life. The affected joints show a doughy spindle-shaped swelling, and the overlying skin may be tight and glossy. In from 15 to 20 per cent of the cases careful search will reveal the presence of painless subcutaneous nodules similar to those which are so characteristic of rheumatic fever. The usual site is the dorsal surface of the forearm a short distance below the olecranon. They vary in size from seed-like bodies to nodules as large as an olive. They may persist for months and years and then disappear. The subcutaneous nodule is not found in osteoarthritis. There are often general signs of chronic infection such as malaise, occasional fever, anemia, palpitation, sweating, and a general toxic appearance. The spleen and lymph nodes may be enlarged, especially in children.

**Etiology.**—An enormous amount has been written regarding the etiology of rheumatoid arthritis, but a lengthy discussion seems unnecessary. There are predisposing and exciting factors. The *predisposing factors* are varied; age, sex, heredity, exhaustion, and metabolic disorders may all play a part. Both jaundice and pregnancy exert a peculiar ameliorating effect on the arthritis. The basal metabolic rate is below normal in 20 per cent of cases. But none of these are fundamental. The *exciting factor* is what really counts, and every year fresh evidence accumulates which points to a chronic infection. In support of this there is clinical, pathological, and bacteriological evidence. (1) The *clinical evidence* consists of the signs of an infection already enumerated; a history of many infections in nose, throat, mouth, gall-bladder, genito-urinary tract, or pelvis; the frequent presence of a definite focus of infection; the immediate improvement which sometimes follows upon removal of such a focus. Over 15 per cent of the cases give a previous history of rheumatic fever, which raises the important question as to whether rheumatoid arthritis may be regarded as a sequel to or a chronic form of acute rheumatism. (2) The *pathological evidence* is the gross and microscopic appearance of the synovial membrane, and the histological structure of the subcutaneous nodule. (3) The *bacteriological evidence* is the finding of bacteria in the joint. This has been the great stumbling block in the past, for although some observers have found organisms, others have found none. Cecil found streptococci in the joint fluid in 65 per cent of cases, and from the regional lymph nodes draining the affected joint Cadham has isolated a pleomorphic organism which appears to have both a bacillary and a coccoid stage in its life history. The reason why streptococci cannot be readily seen in the tissues is that they are usually too scanty. In experimental streptococcal arthritis produced by the intravenous injection of the organisms, incubation of the whole joint brings streptococci to light in practically all the inflammatory lesions (Hadjopoulos and

Burbank). After incubation the organisms are found throughout the synovial membrane, the pannus covering the articular cartilage, the loose connective tissue in the Haversian canals, and the tendons and muscles around the affected joint. It is possible that the different organisms obtained by different workers may eventually prove to be one and the same, and that they may be related to the etiological agent of rheumatic fever. A spontaneous polyarthritis closely resembling rheumatoid arthritis occurs in rats, from which a pleuropneumonia-like organism has been isolated. In autopsies on cases of rheumatoid arthritis it is common to find what appear to be old burned-out rheumatic cardiac lesions, including Aschoff bodies in various stages of development. Rheumatic heart disease was present in 53 per cent of a series of 16 patients (Baggenstoss and Rosenberg). From the evidence at

present available it appears probable that rheumatoid arthritis is a chronic streptococcal infection of the synovial membrane and the periarticular tissues secondary to a primary focus elsewhere in the body, and it is possible that rheumatoid arthritis and rheumatic fever are varied expressions of the same disease.

**Lesions.**—The synovial membrane is primarily affected, so that the disease might be called synovioarthritis in contrast to osteoarthritis. If the joint is opened in the operating room the *synovial membrane* is seen to be congested, edematous, redundant, and swollen so as to form pulpy masses or fringes and tags. (Fig. 494.) Microscopically it consists of vascular granulation tissue infiltrated with leucocytes and mono-



FIG. 494.—Synovial fringes in chronic arthritis.

nuclear cells of various kinds, with sometimes great numbers of plasma cells. The surface may be covered by a thin layer of necrotic material containing leucocytes. The *synovial fluid* is increased in amount and may be cloudy in character owing to the large number of the cells which it often contains. The disease may be arrested at this stage, remaining a mere synovitis. Usually, however, the *articular cartilage* is involved. It is attacked both from above and below. The synovial membrane grows over it from the side, forming a thick vascular covering or *pannus* which becomes adherent to the cartilage and eats it away. The cartilage is also attacked from below by granulation tissue which is formed in the superficial layers of the epiphysis as part of the inflammatory reaction. As a result of this combined attack the cartil-



age is destroyed. Adhesions are formed between the two layers of pannus covering the articular surfaces, and the joint cavity may be obliterated. Fibrous ankylosis of the joint develops and in time the ankylosis may become bony. The *periarticular tissue* shares in the inflammatory swelling and edema. The *muscles* of the part undergo marked atrophy; the extensors of the fingers are especially affected, so that the swollen fingers show a characteristic flexion. It has been shown by Steiner and his associates that this atrophy is the result of an inflammatory nodular polymyositis involving widely separated muscles. These lesions are specific for rheumatoid arthritis, and are similar in nature to those found in the synovia and the subcutaneous nodules. One grim and depressing fact is brought out by these studies, namely, that in the seemingly burnt-out cases with no pain but with extreme stiffness of joints, active inflammatory lesions are still present in the muscles; the fire is still smoldering and by no means extinct. The *subcutaneous nodules* bear a striking resemblance to the similar nodules found in rheumatic fever. There is a large area of central necrosis surrounded by a zone of large mononuclear cells arranged in radial fashion. The arterioles in the surrounding tissue often show obliterating endarteritis and deposits of fibrin under the endothelium. The perineurium of the peripheral nerves may show multiple inflammatory lesions similar in type to the subcutaneous nodules (Freund *et al.*).

The *relation of symptoms to lesions* may be disposed of briefly. The general toxic symptoms are not due to the arthritis, but to the focal infection. The enlargement of the joint is caused mainly by swelling of the soft parts (synovial membrane and periarticular tissue), but excess of synovial fluid may play a minor part. The stiffness of the joint is a natural result of the fibrous adhesions between the two layers of pannus. The pain may be due in part to the inflammatory lesions of the peripheral nerves, but the severe later pains are caused by exposure of the underlying bone when the articular surfaces have been eaten away.

**Osteoarthritis.**—In its typical form this degenerative joint disease differs from rheumatoid arthritis in almost every respect. It is commoner in men than in women, especially the form which affects the hip-joint; it is a disease of the later period of life; there are no general symptoms; there is no evidence of a toxic factor; the large joints are commonly involved, often only one joint; there is no true ankylosis. The hip-joint (*morbus coxæ senilis*) offers an excellent example of the monoarticular form occurring in elderly men. The small joints of the hands and feet may also be involved, and it is in them that the clinical manifestations can be more readily studied. The knuckles become greatly swollen and knobby, and the hand is drawn over to the ulnar side so that the deformity is great. *Heberden's nodes* are often present; these are small bony outgrowths at the sides of the terminal phalangeal joints. In the early stage the node is a soft nodule containing a bead of mucoid material, and arises as the result of degeneration of the peri-

articular soft tissue with subsequent ossification. Movement may be much limited by osteophytic outgrowths, but there is no ankylosis.

**Etiology.**—The cause of the degeneration is unknown. It is a slow involuntary process often associated with marked arteriosclerosis, so that local ischemia may play a part. It is always difficult to form a correct judgment of the relation of trauma to any pathological process, but the common idea that trauma is an etiological factor, especially in hip-joint disease, appears reasonable. If a joint is continually exposed to trauma, as in professional athletes (*e. g.*, baseball catcher) or in the course of a trade, it may show the characteristic changes. Degenerative arthritis appears to be a process associated with the ageing of the tissues of the joints. Similar changes are found in the knee-joint in routine autopsies with increasing frequency with advancing age (Keefer, Parker). Erosion of cartilage in these knee-joints is commonest over areas of contact subjected to the greatest movement, strain, weight-bearing, and injury. As a result of gradual loss of elasticity in the articular cartilage the subchondral bone is no longer protected from the irregular localized effects of weight and pressure, and the changes characteristic of degenerative arthritis result. Age may therefore act in two ways: by reducing the elasticity and by representing trauma spread over a period of years. Similar lesions are present in horses and mules (Callender and Kelser). Loss of cartilage is the primary lesion, followed by bone production which is secondary but has given the name of hypertrophic arthritis to the disease.

	<b>Infective Arthritis</b>	<b>Osteoarthritis</b>
<b>Sex:</b>	Common in female.	Common in male.
<b>Age:</b>	Generally under forty years.	Generally over forty years.
<b>Onset:</b>	Gradual but sometimes acute.	Always gradual.
<b>Joint lesions:</b>	An inflammatory condition of synovial membrane. Early lesions in metacarpo-phalangeal joints and wrists; symmetrical and migratory.	A degenerative condition of cartilage and bone. Early lesions in terminal interphalangeal joints, hips, and knees; often unilateral and fixed.
<b>General symptoms:</b>	Toxic symptoms, fever, loss of weight, anemia, low basal metabolism rate.	No constitutional disturbances.
<b>Local signs:</b>	Local signs of inflammation, marked deformity, extreme atrophy of muscles, swelling of soft parts, subcutaneous nodules, fibrous or bony ankylosis. Marked pain. Complete crippling in 10 per cent.	No local inflammation, deformity not marked, muscular atrophy only from disuse, soft parts not swollen, Heberden's nodes and no true ankylosis. Little or no pain. Complete crippling rare.

**Lesions.**—Osteoarthritis is a degeneration of articular cartilage and bone; in this it differs from rheumatoid arthritis which is primarily an inflammation of synovial membrane. The *cartilage*, both its cells and matrix, degenerate, and the smooth surface becomes roughened like the pile of velvet. The cartilage cells swell, burst, and disappear, and the matrix undergoes a perpendicular fibrillation which accounts for

the velvety surface. The softened cartilage is gradually worn away until the underlying bone is exposed. In a hinge joint (elbow, knee) the process of attrition is irregular, so that parallel furrows and ridges are formed. The periphery of the cartilage has a much better blood supply than the central part and survives the general downfall. The bone degenerates together with the cartilage, but the exposed surface undergoes a curious process of condensation and hardening, as a result of which it becomes polished like ivory. This appearance is known as *eburnation* (*eburneus*, ivory), and no really satisfactory explanation of the process can be given at present. Deep to the condensed layer the bone is degenerated, rarefied, and becomes absorbed, so that the greater part of the head and neck of the femur may disappear. In addition to central atrophy there is peripheral proliferation. Cartilaginous excrescences are formed at the margin of the articular cartilage which resemble candle drippings and cause lipping of the edge of the joint. They increase the available articular surface and may be compensatory in character. They tend to become ossified and osteophytes are also formed farther out, so that the atrophied head of the bone is surrounded by a ring of excrescences which greatly limit movement. It is because of these changes, which form a striking feature in the roentgen-ray picture, that this variety is sometimes called by the misleading name of the hypertrophic form of chronic arthritis. The *synovial membrane* may become fibrous and fatty, and sometimes presents shaggy fringes which may be changed into cartilage and become detached to form the foreign bodies known as *joint mice*. The *ligaments* share in the general degeneration and dissolution, so that dislocation may occur finally.

**Anchylosing Spondylitis (Marie-Strümpell).**—The chronic disabling disease of the spine known as Marie-Strümpell spondylitis is perhaps more nearly related to rheumatoid arthritis than to osteoarthritis. It is, however, very much commoner in males (15 to 1), usually beginning before the age of thirty. The etiology is unknown, but certain features suggest a chronic infection, *viz.*, low grade fever, tachycardia, high sedimentation rate, weight loss and wasting of muscles. Little has been added to our knowledge of the condition since the classical paper of Pierre Marie in 1898.

The essential *lesions* occur in the joints of the vertebral column. There is a synovitis, with increased vascularity, proliferative changes in the synovia, and infiltration of the tissues with lymphocytes and plasma cells. Later the articular cartilage is destroyed, fibrous adhesions are formed, and there is eventual bony fusion. Some of the earliest and most characteristic changes occur in the sacro-iliac joints, which may be demonstrated long before the onset of symptoms in the back. There is destruction and narrowing of the joint space, which appears in Roentgen films as a fuzziness of the opposed surfaces of the bones. Late in the disease there is calcification followed by ossification of the various vertebral ligaments including the anterior spinal ligament and finally the intervertebral discs with bony ankylosis. The

condition now is well described by the term "poker back." The rigidity is extreme, the normal spinal curvatures are lost, and the cervical spine is curved into a bow which forces the miserable man's head down until his chin touches his chest. The state of the patient when these changes are complete can be better pictured than described.

Although the progress of the disease may be as relentless as described, the process may be arrested at any stage. Involvement of the large peripheral joints (hip, knee, shoulder, etc.) occurs in 15 to 25 per cent of cases, the lesions closely resembling those of rheumatoid arthritis. Whether the disease is merely a special expression of rheumatoid arthritis or is a separate pathological entity remains a matter of dispute. Whilst the condition resembles rheumatoid arthritis in many respects, the calcification of ligaments, predominance in males, lack of response to gold therapy and infrequency of streptococcal agglutinins in the blood are quite distinct from that disease.

**Charcot's Disease.**—The peculiar condition known as Charcot's disease of joints may develop in the course of tabes dorsalis and occasionally it complicates syringomyelia, so that it has been called a neuropathic arthropathy. It may develop at a fairly early stage of tabes, and usually affects the large joints of the lower limb (hip, knee, and ankle) owing to the preponderatingly lumbar distribution of the tabetic lesions in the cord. In syringomyelia it is more common in the upper limb for a similar reason. As a rule only one joint is involved. The onset is insidious, but the patient may suddenly discover that the joint is much swollen. This swelling may develop quite rapidly. The further progress is a story of destruction and disintegration until the joint may be completely disorganized and flail-like, so that a hinge joint like the knee or elbow can be moved in every direction. Although grating and crunching can be felt in the joint there is a complete and remarkable absence of pain. Sometimes the process of destruction is very rapid, reaching its maximum in the course of a few weeks, after which the disease may become stationary. The head of the femur has been known to disappear in the course of six weeks. This quickness of action, so unlike ordinary osteoarthritis, is one of the most puzzling features of the disease. The *lesions* are essentially degenerative and destructive, especially in the acute cases where it would appear as if some powerful solvent had dissolved away first the articular surface and then the bone, leaving a ragged stump and disconnected fragments. The synovial membrane may develop villous and polypoid tags. When the acute stage is past numerous osteophytes may form a fringe around the joint and in the capsule. It seems probable that during the stage of attrition large numbers of osteoblasts are set free in the joint cavity and become implanted in the capsule and periarticular tissues where they form new bone. The *nature of the condition* is very obscure. The pathology does not remotely resemble that of syphilis. It is commonly supposed to be due to loss of hypothetical trophic influences to the joint on account of the cord lesion. It appears more probable that a loss of joint sensibility which may develop both in tabes and syringo-

PLATE XXX



Tuberculous Arthritis

*(Boul's Surgical Pathology, courtesy of W. B. Saunders Company.)*



myelia exposes it to trauma and attrition which in some obscure way bring about the rapid osteoarthritis characteristic of Charcot's disease.

**Hemophilic Joint.**—In hemophilia an osteoarthritis may develop as the result of repeated hemorrhages into one of the large joints. The cartilage becomes eroded and fibrillated, the bone is exposed, periarticular osteophytes are formed, and the synovial membrane is thickened and fringed.

### TUBERCULOSIS OF THE JOINTS

Tuberculosis of the joints is a disease of children, and is usually secondary to tuberculosis of the adjacent bone. When it occurs in an adult it is more likely to be primary in the synovial membrane, infection being carried by the blood stream from some distant focus. Bone tuberculosis has a strong tendency to spread to the corresponding joint, so that bone and joint tuberculosis are commonly combined. The bone lesion is in the metaphysis close to the epiphyseal cartilage, and from there the infection spreads outward along the vessels and reaches the synovial membrane. Or it may destroy the epiphyseal cartilage, invade the epiphysis, penetrate the articular cartilage, and in this way reach the joint. Trauma is said to be a predisposing factor, but as usual this is difficult to prove. The joints commonly affected are the hip and knee, followed by elbow, shoulder, and ankle.

**Lesions.**—All the joint structures and the adjacent bone are involved if the disease is not arrested, but in the adult the main lesion may be a tuberculous synovitis for a considerable time. The *synovial membrane* may resemble that of rheumatoid (infective) arthritis, but is even thicker and more voluminous, so that it may fill the entire cavity. It is gray in color and may show tubercles on the surface or only when the mass is incised. (Plate XXX.) Gelatinous degeneration is common and caseation may occur in the late stages. Microscopically it usually presents a classical picture of tuberculous granulation tissue with epithelioid tubercles and numerous giant cells. The *fluid* is usually scanty but highly fibrinous, so that it contains flakes of fibrin which may develop into foreign bodies known as *melon-seed bodies* or *rice bodies*. Occasionally there is abundant serous effusion (hydrops) with comparatively little synovial thickening; in these cases there may be large numbers of melon-seed bodies. The *articular cartilage* is attacked both from above and below, just as in rheumatoid arthritis. The synovial membrane, or rather the granulation tissue into which it is converted, creeps over the articular surface, becomes adherent to it, and sends vessels into it, so that the cartilage becomes eaten away and the underlying bone is exposed. (Fig. 495.) The cartilage is also attacked by granulation tissue from below, and instead of being eaten away it may become separated in flakes or even as a complete cast of the articular surface. The *bone* shows the rarefying osteitis which has already been studied in connection with tuberculosis of bone. The initial lesion is in the red marrow, and the absorption of bone is really secondary. The *periarticular soft parts* are involved later. The liga-

ments are softened and finally destroyed, so that the joint may be dislocated. The muscles and other periarticular tissue undergo gelatinous degeneration, a change which is largely responsible for the *white swelling* so characteristic of tuberculous arthritis. When the gelatinous tissue undergoes caseation and liquefaction a tuberculous abscess (cold abscess) is formed, the contents of which are not true pus but liquefied necrotic tissue. If this is opened or perforates the skin, the whole picture is changed, and mixed infection runs riot through all the tissues in and around the joint. *Caries sicca* is a rare form of the disease which usually affects the shoulder-joint and pursues a slow course with no effusion, quiet absorption of the bone, and the formation of dense fibrous adhesions.



FIG. 495.—Tuberculosis of the knee-joint. The articular cartilage of the femur is eaten away and the underlying bone is eroded.

The *termination* is very variable. At almost any stage the disease may be arrested. This may result in mere stiffness, but when the articular surface is destroyed there will be fibrous or bony ankylosis. Amyloid disease may complicate prolonged secondary infection, or general miliary tuberculosis may terminate the picture.

**The Relation of Symptoms to Lesions.**—Pain, an early and constant symptom, is due to erosion of the articular cartilage. It is worse when the patient drops off to sleep, because then the watchful muscles which hold the joint rigid are off their guard. The joint is swollen and has a characteristic fusiform contour. Much of the enlargement is caused by the swelling of the synovial membrane, but in the later stages the gelatinous swelling of the periarticular soft tissues plays a part. Limitation of movement, the earliest physical sign, is a natural sequel to any inflammatory lesion in a joint. Muscular spasm is an attempt to keep the part at rest. Early atrophy of the surrounding muscles is partly due to disuse, but part of it may be due to the action of toxins.

**Syphilis of the Joints.**—Compared with tuberculosis, syphilis of joints is of little clinical importance. In the *secondary* stage there may be an effusion into a joint, especially the sterno-clavicular. In *tertiary* syphilis the changes may resemble those of tuberculosis, *i. e.*, swelling of the synovial membrane, erosion of the cartilage, and gummatous formation in the periarticular tissue, so that a "white swelling" may develop similar to that of tuberculosis.



## GONORRHEAL ARTHRITIS

This important form of arthritis occurs in about 2 per cent of cases of gonorrhea. The infection is due to spread by the blood stream. As Osler remarks, variability and obstinacy are the two most characteristic features of the disease. The joint infection usually occurs about the end of the third week, but it may not set in for some months after the original urethral infection. The disease is a polyarthritis, but it is usually confined to a few of the large joints, of which the knee is the most frequent sufferer. The arthritis may be acute or chronic.

(1) The acute variety takes the form of an acute synovitis, with heat, redness, and swelling of the joint and much pain. There may be a moderate amount of turbid effusion. As in the acute arthritis of rheumatic fever, there is no destruction of tissue, so that when the inflammation resolves there is no permanent stiffness of the joint. (2) In milder cases there is a hydrarthrosis, usually limited to one joint which becomes distended with serous fluid. (3) Finally, there is a chronic and persistent arthritis due to a low-grade infection. This is the commonest form, and owing to the chronicity of the infection fibrous adhesions may form, leading to permanent stiffness of the joint.



FIG. 496.—Melon-seed bodies in a joint.

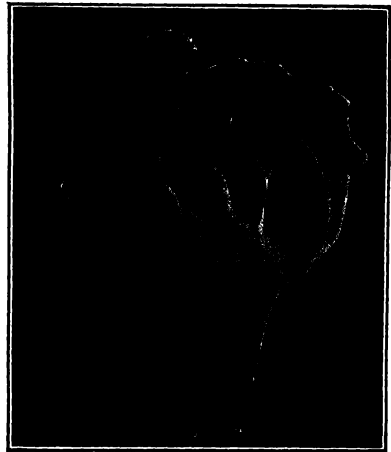


FIG. 497.—Cyst of external semilunar cartilage.

**Loose Bodies in the Joints.**—Three forms of loose bodies in joints may be found in such conditions as tuberculosis, osteoarthritis and Charcot's disease, and loose bodies may occasionally occur in an apparently normal joint. These three varieties are fibrinous bodies, fibrous and fatty bodies, and cartilaginous bodies. (1) *Fibrinous loose bodies* occur chiefly in tuberculous joints, and also in synovial sheaths and bursæ affected by tuberculosis. They take the form of small, round or oval bodies like melon-seeds or rice-grains, and may be present in large numbers. (Fig. 496.) It is difficult to say if they are formed as the result of some fibrinous change on the surface of the synovial membrane or if they are deposited from fluid rich in fibrin. (2) *Fibrous and fatty loose bodies*

are formed from villous tags of synovial membrane which become detached in tuberculous arthritis and osteoarthritis, in both of which conditions the membrane is often marked by numerous fringes. Some of the bodies may still be attached by a slender pedicle. (3) *Cartilaginous loose bodies* may arise in three different ways. (a) A cartilaginous osteophyte may be detached in osteoarthritis and particularly in Charcot's disease. (b) A loose body occurring in an otherwise normal joint has always been a puzzling phenomenon, but it appears probable that it is a fragment of articular cartilage which has become detached as the result of direct trauma or of muscular or ligamentous strain. (c) Synovial chondromata may develop in tags of synovial membrane and become detached.

**Cysts Connected with Joints.**—The cyst may or may not communicate with a joint. A cyst in the neighborhood of a joint is likely to fall into one of three groups. (1) *Cysts due to distention of a bursal sac* which may or may not normally open into the joint cavity. (2) *Cysts formed by hernial protrusion of the synovial membrane through gaps in the capsular ligaments.* Such a cyst is called a *Baker's cyst*, which almost always develops in connection with the knee, appears in the popliteal space, and may make its way down the leg after the manner of a cold abscess. (3) *Cysts of the semilunar cartilages of the knee,* usually the external, occasionally the internal. (Fig. 497.) The cyst is multilocular, the contents are gelatinous, and a preceding history of trauma is common. Some of the cysts may have an endothelial-like lining. The lesion appears to be the result of a gelatinous degeneration of the fibro-cartilage with cyst formation, so that the pathogenesis is similar to that of ganglion (page 1009). The cyst lining is probably formed by modified fibroblasts. Some writers believe that the cysts are developmental in character, arising from portions of the synovial membrane included in the semilunar cartilage.

### TUMORS OF JOINTS

**Synovial Sarcoma.**—This rare tumor arises from the specialized connective-tissue cells which line the sheath. The joint cavity is filled with soft, fleshy, vascular processes which seem to arise from many parts of the lining. The microscopic picture varies. The cells may be spindle-shaped or cuboidal; if the latter they may surround pseudoglandular spaces or be arranged in nests suggesting epithelium. The tumor is radioresistant and metastasizes to the lungs.

**Giant-cell Tumor.** The lesion resembles giant-cell tumor of bone, but is less destructive and is marked by the presence of numerous lipid-filled xanthoma cells.

### LESIONS OF THE INTERVERTEBRAL DISCS

Interest in the pathology of the intervertebral discs dates from the work of Schmorl of Dresden in 1925. Each disc consists of: (1) the nucleus pulposus, a highly elastic semi-fluid mass compressed like a spring between the vertebral surfaces; (2) the annulus fibrosus which surrounds and confines the turgid nucleus; (3) the cartilage plate which separates the nucleus from the vertebral body. Lesions may develop in any of the three constituents. Owing to man's upright position the discs are subjected to constant strain for which they were not originally intended, so that degeneration in later life is commoner than in any other organ, with corresponding loss of the normal cushioning function. The three chief pathological conditions related to the discs are herniation, posterior displacement, and spinal deformity.

*Herniation of the nucleus pulposus* into the spongiosa of the vertebral bodies may be due to lesions of the cartilage plate or the bone. As the result of tearing of the cartilage plate (as in compression fracture) or degeneration of the plate due to age the turgid nucleus bulges into the body of the vertebra. Osteoporosis of the vertebræ allows multiple protrusions to occur. These lesions, which are known as Schmorl's nodes, are very common and usually of no clinical significance.

*Posterior displacement* of the nucleus into the spinal canal, commonly called *prolapse*, is due to degeneration of or injury to the annulus fibrosus. In the past the prolapsed disc has been mistaken for chondroma or myxofibroma. As a rule the prolapse causes no symptoms, but when it occurs between the fifth lumbar vertebra and the sacrum or between the fourth and fifth lumbar vertebræ it may press on the fifth lumbar or first sacral nerve roots causing first low back pain and later sciatica. The symptoms are relieved by removal of the displaced portion of disc.

*Spinal deformities* related to disc pathology fall into three groups: (1) juvenile kyphosis, (2) senile kyphosis, and (3) spondylitis deformans. *Juvenile or adolescent kyphosis* occurs in boys, and is associated with a series of prolapses of nucleus pulposus through ruptured cartilage plates, probably due to congenital weakness of the plates. There is loss of disc substance most marked anteriorly, with consequent pressure in that area and interference with growth, so that the vertebræ become wedge-shaped and kyphosis results. *Senile kyphosis* is caused by degeneration and destruction of the anterior part of the discs. *Spondylitis deformans* usually takes the form of osteoarthritis of the spine, the typical senile spinal disease. Degeneration of the annulus allows the discs to press on the intervertebral ligaments, thus exerting a pull on the periosteum to which the ligaments are attached. The continued pull leads to overgrowth of the bone at the margins of the vertebræ with the formation of osteophytes, lipping, and limitation of movement. In the Marie-Strümpell type of spondylitis the discs are converted into bone and fuse with the bodies of the vertebræ; the result is complete rigidity, the poker back.

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## CHAPTER XXXIV

### THE MUSCLES, TENDONS, AND BURSÆ

THERE are some points in connection with the histology of muscle which must be kept in mind, else normal appearances may be mistaken for the lesions of disease. If fresh muscle newly removed from the living body, as in a surgical operation, is at once placed in a fixative such as formalin, the fibers may appear wavy and distorted, and the contents are broken up so that part of a fiber may present an appearance of a hyaline structureless lump, while another part appears empty. These changes are due to the contractility of the fiber, and they can be obviated by keeping the muscle in the ice-box, as is done with autopsy material. For differences in the finer histological detail before and after rigor mortis as shown by special muscle stains, Miller's paper may be consulted.

The voluntary muscles are seldom the seat of pathological processes. Those which do occur may be divided as follows: (1) atrophic changes, (2) degenerative changes, (3) inflammatory changes, (4) fibrotic changes, and (5) tumors. A muscle consists of interstitial connective tissue as well as muscle fibers, and much of the pathological change affects this tissue.

**Atrophic Changes.**—Atrophy of a muscle may be due to disuse, to joint disease or to nerve lesions. (1) The *atrophy of disuse* is a commonplace observation. The fibers shrink in size, and if the disuse is permanent the contractile substance may be converted into fibrous and fatty tissue. (2) The *atrophy which accompanies chronic disease of a joint, e. g., tuberculosis or rheumatoid arthritis*, is partly due to disuse, but the atrophy may be so extreme that it seems probable that some other factor must play a part. This may be a local toxic action, or sensory impressions may pass from the diseased joint to the cord and there induce changes in the motor cells of the anterior horn. (3) *Neuropathic atrophy* is seen in injuries of motor nerves, acute poliomyelitis, and progressive muscular atrophy. It is evident that in all these conditions disuse will play a part in producing the atrophy, but in addition there may be a loss of hypothetical trophic impulses to the muscles. The electrical "reaction of degeneration" is present in these cases.

**Degenerative Changes.**—As long ago as 1863, Zenker described the degeneration of muscle in typhoid fever which goes by his name. Zenker's degeneration is a hyaline change, most commonly seen in the rectus abdominis and the muscles of the abdominal wall, but also in the diaphragm and the voluntary muscles elsewhere. A similar change may complicate the pneumonia of epidemic influenza and that follow-

ing epidemic measles, but in these cases the change is confined to the rectus abdominis. The affected part of the muscle becomes pale, undergoes a massive hyaline degeneration, as a result of which it becomes remarkably fragile, so that rupture is common, and this may be accompanied by hemorrhage and the formation of a hematoma. If organisms are circulating in the blood, they may infect the hematoma and cause abscess formation in the abdominal wall. *Microscopically*, the first change is a hyaline swelling of the contractile substance, followed shortly by a remarkable nuclear proliferation, the new cells sometimes filling the sarcolemma sheath, and being concerned with the removal of the degenerated muscle. There is rapid loss of the transverse and longitudinal striations, and the fiber becomes amorphous, homogeneous, and highly refractile. Vacuoles may appear in the fiber, and the hyaline material may become granular.

*Regeneration* of muscle after this hyaline degeneration may be remarkably complete, and the entire muscle may be renewed. The hyaline clumps become surrounded by phagocytes which fill the sarcolemma and remove the débris. At the same time the remaining muscle nuclei of the old fiber multiply and produce new muscle cells. This complete regeneration is not seen in wounds of muscle, especially where a piece has been excised. In such a case there is partial regeneration at the edge of the gap, but most of the union is due to fibrous tissue.

**Inflammatory Changes.**—Acute inflammation of muscle is not common. It affects the interstitial tissue, with secondary destruction of the muscle fibers. The infection may spread from a suppurating wound, or small abscesses may be formed in the muscle in the course of pyemia. In rare cases an *acute suppurative myositis* appears in an otherwise healthy patient, a condition analogous to acute osteomyelitis in a bone. Here the inflammation is limited to a single muscle, the pus being confined within the sheath of the muscle. *Acute poly-myositis* is a rare form of severe non-suppurative inflammation of many muscles of unknown origin. The muscles are hard, swollen, and extremely painful and tender. They show round-cell infiltration with areas of liquefaction. Tuberculosis, syphilis and actinomycosis may in rare cases produce in muscles the lesions characteristic of those infections. The inflammatory lesions caused by trichiniasis are described elsewhere. A rare condition easily mistaken for trichiniasis is *dermatomyositis*, a non-purulent myositis associated with inflammation of the skin. The skin, subcutaneous tissue and muscle are edematous and infiltrated with lymphocytes and plasma cells. There is tenderness, pain on movement, and erythema of the overlying skin. The prognosis is bad.

**Fibrotic Changes.**—Under this general heading may be considered myositis ossificans, myositis fibrosa, and congenital torticollis.

**Myositis Ossificans.**—There are two kinds of so-called ossifying myositis, which bear no relation to one another. They are the traumatic and the progressive forms. *Traumatic myositis ossificans* is a not uncommon condition which may be the result of repeated injury to a muscle or a single severe injury, especially when accompanied by hemorrhage. A good example is the development of bone in the adductor muscles of the thigh in riders. It is possible that osteoblasts are detached as a result of the trauma and become implanted

in the muscle where they form bone, but it is also possible that there may be a metaplasia of fibrous tissue into bone, especially when there has been hemorrhage and tissue destruction. The formation of bone which occasionally takes place in the edges of a laparotomy wound might be explained on this basis. The great practical importance of the condition is the danger that it may be mistaken for an osteogenic sarcoma of bone invading the muscle.

**Progressive Myositis Ossificans.**—This is a very rare progressive disease, which commences in childhood and slowly kills the patient. The first lesions take the form of doughy and sometimes painful swellings, particularly in the muscles of the back and neck. These swellings subside, leaving areas of fibrosis in which bone is gradually formed. The progress of the disease is marked by exacerbations and remissions. Large bony plates are formed, and the body may finally be enclosed in a sheath of bone which makes all movement impossible and leads to the death of the patient from respiratory paralysis. The disease appears to be some obscure disorder of the bone-forming power of the tissues, for congenital bony defects such as microdactylia in the hand and absence of a phalanx in the great toe are often present.

**Progressive Myositis Fibrosa.**—This is another very rare condition, much less well recognized than myositis ossificans, but essentially similar in nature. Many muscles of the back and upper limbs develop swellings in part or the whole of the muscle, more especially at the attachments. The swelling is hard, diffuse and painless. In a few days it decreases in size and becomes harder and this induration is permanent. The swelling may suddenly recur, as in the case of myositis ossificans. Microscopically there is a marked general increase in the fibrous tissue of the muscle, with degeneration and disappearance of the muscle fibers. There is a notable absence of round-cell infiltration. It seems probable that the disease is identical with myositis ossificans, with the exception that in the latter disease the new-formed fibrous tissue becomes converted into bone.

**Congenital Torticollis.**—Congenital torticollis may be regarded as the result of a localized form of myositis fibrosa which usually develops about the age of four years. In these cases the history goes back to the so-called "sternomastoid tumor of infancy," which generally appears about ten days after birth. A spindle-shaped swelling develops in the sterno-cleido-mastoid; this is peculiarly hard and feels like cartilage. The swelling persists for two or three months and is then gradually absorbed, disappearing entirely in four to six months after birth. If the muscle is now excised it is found to consist entirely of fibrous tissue with complete replacement of the muscle fibers. The neck lengthens rapidly in the fourth year, and as the fibrosed muscle is unable to grow, the head is pulled over to that side—a condition of congenital torticollis. Middleton has shown that the sterno-cleido-mastoid tumor is produced as the result of acute venous obstruction due to pressure on the veins during labor, rendered permanent by thrombosis of the veins. When the artery to a muscle is tied experimentally or the artery and vein together, the result is simple atrophy. But when the vein above is tied, the arterial supply being left intact, the muscle becomes acutely swollen, hard and tender, and very cyanosed. The fibers disintegrate and the muscle is densely infiltrated with round cells. In the course of a few months such a muscle is completely replaced by fibrous tissue. When the vein alone is obstructed the autolytic products from the breaking down muscle fibers are not carried away from the part and appear to stimulate proliferation of fibroblasts. The marked edema of the muscle also favors the formation of fibrous tissue.

**Dupuytren's Contraction.**—Owing to thickening, hardening and shortening of the palmar fascia the fingers may become progressively flexed on the palm, so that normal use of the hand is impossible. The etiology is unknown. The

microscopic picture is one of active proliferation of fibroblasts which may be mistaken for fibrosarcoma, with dense collagen formation.

**Volkman's Contracture.**—This condition, called originally by Volkmann ischemic contracture, usually occurs in young people and affects the muscles of the forearm. It is commonly associated with the pressure of splints or a tourniquet or with hemorrhage resulting from a fracture. Within a few hours of the receipt of injury burning pain develops in the hand or forearm. This is followed by contracture of the fingers which become fixed in the flexed position. If the muscle is exposed when the condition is fully developed it is hard, homogeneous, yellowish in color and is not recognizable as skeletal muscle. Microscopically the nuclei and cross striations are lost, there may be an infiltration of inflammatory cells and phagocytes at the margin of the area, and the picture is one of infarct, similar to that of a cardiac infarct. Later the part becomes fibrosed.

Volkman originally (1872) believed that the cause of the condition was direct pressure on the arteries. In 1914 the ischemic theory was given up, and the view substituted that venous obstruction was the causal factor (J. B. Murphy). A return has now been made to the idea that the condition is essentially ischemic in nature, due usually to arterial spasm resulting from injury to the wall of the vessel (Griffiths). An identical picture, both pathological and clinical, can be produced in the rabbit by ligating the arteries to a limb.

**Fibrositis.**—Reference may be made in this place to the subject of fibrositis, commonly called muscular rheumatism. In this condition chronic inflammatory foci are found not only in the muscles, but also in the subcutaneous tissues, nerve sheaths, periarticular structures, etc. At first there is an acute inflammatory edema with swelling of the connective-tissue fibers; the center of the lesion may be necrotic. Any cellular exudate is slight and lymphocytic in type; polymorphonuclears are absent. The tension caused by the localized edema irritates the nerve endings, and muscular movement (as in sciatica, stiff neck, etc.) may be accompanied by intense pain.

**Tumors.**—Tumors of striated muscle, either primary or secondary, are remarkably rare. Primary tumors may be myoblastoma or rhabdomyoma. *Myoblastoma* consists of round or elongated cells in ribbons or bundles; they have the strongly acidophilic cytoplasm of muscle fibers, but no transverse striations or only very faint striations shown by iron hematoxylin. Large multinucleated syncytial masses may be present. The most characteristic feature of the cells is their markedly granular cytoplasm, so that they have been called granular-cell myoblastoma. It is by no means certain that these tumors arise from myoblasts, for they are found in sites devoid of striated muscle, as well as in the substance of such muscle. The most common site is in the tongue and mouth. The tumors are benign, a further argument against their origin from primitive muscle cells, especially as tumors consisting of striated fibers are markedly malignant. *Rhabdomyoma* consists of fully striated fibers. It occurs in the heart, bladder, vagina and cervix, and is highly malignant. On mucous surfaces, such as bladder and vagina, it tends to be lobulated and polypoid.

**Myasthenia Gravis.**—This rare and mysterious disease is characterized by great weakness, most marked in the muscles of the face, but shared to a lesser degree by the other muscles. Nothing is found in the affected muscles or in the nervous system to account for the myasthenia. It is true that the muscles show a marked degree of infiltration with small round cells, but there is no atrophy of the fibers, and similar infiltrations of small cells are found in the liver, adrenals and other organs. The meaning of these infiltrations is quite obscure, but there is hyperplasia of the thymus in 50 per cent of the cases. Definite thymomas have been described, and there may be thyroid hyperplasia. All this suggests a possible endocrine basis for the disease. The myoneural junction is the probable seat of the trouble. Normal excitation transmission at this junction depends on the liberation of acetylcholine, and probably is con-



ditioned by endocrine activity. Prostigmine acts on the myoneural junction, and is very valuable in treatment of the disease. The occasional association of thymic tumors with myasthenia gravis suggested to Blalock the possibility that removal of the thymus, even though no tumor was present, might be beneficial, a hope which has been abundantly satisfied. A number of the cases recovered so completely that it was possible to discontinue the prostigmine.

## THE TENDONS

**Tenosynovitis.**—The tendons are non-vascular and therefore immune from inflammation, but the tendon sheaths at the wrist and ankle are often infected. All the usual forms of inflammation are met with in the tendon sheaths. *Traumatic tenosynovitis* occurs in piano-players, typists, and others whose tendons are subjected to excessive use. Fibrin is laid down on the wall of the sheath and the surface of the tendon, so that cracking is felt when the tendon is used. If effusion occurs, an elongated swelling appears in the line of the tendon. *Suppurative tenosynovitis* may result from spread of infection from a septic process in the fingers. *Gonorrheal tenosynovitis* may be dry, serous, or suppurative. *Tuberculous tenosynovitis* resembles tuberculous arthritis. There may be an abundant formation of tuberculous granulation tissue causing a "white swelling" like that seen in tuberculosis of a joint. Or there may be abundant serous effusion (hydrops) with only limited production of granulation tissue, but abundant deposits of fibrin which are rubbed off by the play of the tendon, so that large numbers of melon-seed bodies are formed.

**Ganglion.**—This is a cystic swelling which develops in connection with a tendon sheath. The common position is the back of the wrist, but it may occur on the back of the foot and rarely on the outer aspect of the knee. It is attached to the tendon sheath or the joint capsule, but does not communicate with these cavities. It appears to commence as a proliferation of the connective tissue of the sheath; this undergoes mucoid degeneration with the formation of numerous small cysts which fuse to form one large cyst filled with soft mucoid material. Although we have spoken of a cyst, it is not a true cyst, for there is no endothelial lining. The condition known clinically as *compound palmar ganglion* is a tuberculous tenosynovitis.

## THE BURSÆ

A bursa, which is a sac lined by synovial membrane and containing synovial fluid, may be the seat of inflammation or tuberculosis. *Traumatic bursitis* is usually caused by chronic and repeated irritation ("housemaid's knee," "student's elbow"), but occasionally it is due to a blow. The bursa is distended with serous fluid (hydrops), and in course of time the wall becomes thickened and covered with ridges and tags. The latter may be detached, forming melon-seed bodies.

*Infective bursitis* is caused by a perforating wound or direct spread of infection from the adjacent joint. *Tuberculous bursitis* may take the form of hydrops with melon-seed bodies, or the bursa may be filled with granulation tissue, which eventually undergoes softening and liquefaction.

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## CHAPTER XXXV

### DENTAL PATHOLOGY

ALTHOUGH the care of the teeth belongs to the dental profession, the well-educated doctor should know at least something of the principal diseases of these structures, notably caries, periapical abscess, and pyorrhea alveolaris. A mere outline of these conditions is all that is attempted in the following pages.

**Anatomical Considerations.**—The teeth are homologous to the dermal scales of certain fishes, and to such appendages of the mammalian skin as the hair and nails. A hair is a horny structure composed of epithelial cells resting on a papilla of connective tissue containing bloodvessels and nerves. A tooth is a calcified structure formed by epithelial cells resting on a papilla of connective tissue; the outer part of this dental papilla becomes calcified to form the dentine, the inner part remaining as the dental pulp supplied with vessels and nerves.

A tooth is composed of four structures: (1) enamel, (2) dentine, (3) pulp (the formative tissue of the dentine), and (4) cementum. The *enamel* is the hardest of animal tissues, but it is brittle and easily fractured. The *dentine* forms the main bulk of the tooth; it is strong and elastic, therefore not readily broken. Such a specialized tooth as the elephant's tusk consists of dentine without any covering of enamel, as it is designed for digging and fighting, functions for which toughness is needed and brittleness is undesirable. The dentine is traversed by great numbers of fine channels known as the dentinal tubules which pass from the pulp outward to the inner surface of the enamel and cementum. As the dentine is formed from the dental connective tissue papilla it is mesodermal in origin. The *pulp* represents the remains of the formative organ of the dentine. The outer layer next the dentine contains specialized tall columnar connective cells, the odontoblasts, with long cytoplasmic fibrils which extend into the dentinal tubules; these are the only columnar connective-tissue cells in the body. In addition to the odontoblasts, the pulp contains numerous ordinary connective-tissue cells and abundant bloodvessels, lymphatics, and nerves. The nerves end around the odontoblasts, but do not penetrate into the dentine, so that the odontoblasts form a connecting link between the sensitive dentine and the nerves. The nerves of the pulp respond in only one way when the dentine is stimulated by touch, heat or cold, and that is by pain. It is evident from what has been said that the constitution of the pulp enables that structure to develop a marked inflammatory reaction against bacterial infection, whereas no such reaction is possible in the avascular and acellular dentine and enamel. The *cementum*, which closely resembles bone histologically,

covers the dentine in the root portion of the tooth, and meets the enamel at the gingival line. It furnishes an attachment for the strong connective tissue fibers which fasten the root of the tooth to the bone of the alveolus. The *peridental membrane* or *pericementum*, which may be regarded as the periosteum of the tooth, is the fibrous connection between the bone and the cementum of the root. It is abundantly supplied with nerves which are responsible for the sensation felt when the tooth is touched. Atrophy of this membrane is followed by loosening of the tooth in its socket. Its normal functions may be summarized as nutrition, retention, and cushioning.

### CARIES

Caries or dental decay is the most prevalent of all the diseases of the teeth. It has existed from prehistoric and early historic times. It is found in the teeth of Egyptian mummies. It is world-wide in its distribution, but certain races are remarkably exempt, *e. g.*, African natives and Eskimos. When these peoples adopt civilized customs, however, they tend to develop caries. The etiology of caries is a singularly complex subject involving a large number of factors both local and constitutional, a consideration of which will be postponed until the process itself has been described. Caries is primarily a disease of childhood, adolescents and young adults. The greatest susceptibility is at the period of the eruption of the teeth, the maximum incidence being in the interval of transition from the deciduous to the permanent teeth. The disease is commonest in the molars, then the upper incisors, then the bicuspid; the lower incisors and canines are rarely affected.

**Lesions.**—Dental caries is a unique process, unlike any other in human pathology. It must not be confused with caries of bone, which is an inflammatory reaction to infection, for we have already seen that neither the enamel nor the dentine contains the vessels and connective-tissue cells without which an inflammatory reaction is not possible. The tissues affected by caries are the enamel, the dentine, and the cementum, with secondary infection of the pulp. The enamel consists almost wholly of inorganic material (salts), whereas the dentine consists of 30 per cent organic matter (collagen and elastin). The pathogenesis of cavity formation in these two structures will differ accordingly. The mineral salts of the enamel are soluble in acids, and it is by acids that they are dissolved in caries. These acids are produced from the carbohydrates of the food by acid-forming bacteria, and the opportunity for the acids to act is afforded by the presence of fissures or defects on the occlusal surface. (Fig. 498.) In other cases the process commences on the lateral surface at the point of contact of two contiguous teeth, both of the teeth being commonly affected. The acid (lactic, malic, formic, acetic) dissolves the cement substance of the enamel at the bottom of the fissure, and a localized area of disintegration is produced which is wedge-shaped, with the apex at the surface

and the base toward the enamel-dentine junction. When the process reaches the dentine it proceeds more rapidly and more widely, spreading laterally along the line of junction owing to the branching of the

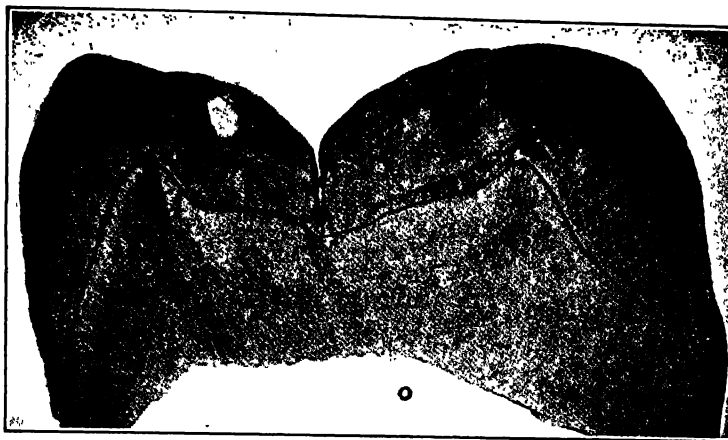


FIG. 498.—Deep fissure in enamel of occlusal surface. (Noyes.)

dentinal tubules, and deeply into the dentine along the line of these tubules. The inorganic matter is here also dissolved, and again the area of disintegration is wedge-shaped, but this time with the base at the enamel-dentine junction and the apex toward the pulp. The bacteria spread readily along the dentinal tubules, so that the pulp is always potentially infected in every case in which the dentine is involved. (Fig. 499.) The organic matrix of the dentine is digested by proteolytic ferments of bacteria, which are either the original invaders or organisms of another group representing a secondary infection. As a result of the combined process a large area of dentine may be destroyed with the formation of a cavity of considerable size, although the original lesion in the enamel may still be quite small. Eventually the remainder of the enamel may cave in, resulting in a sudden marked enlargement of the cavity. The process is a steadily progressive one, as neither the enamel nor the dentine is capable of resistance or repair, although a formation of



FIG. 499.—A drawing showing the microorganisms of caries growing through the dentinal tubules. (G. V. Black.)

"secondary dentine" may be laid down between the dentine and the pulp, reducing the size of the pulp cavity; even this reaction is impossible in a devitalized tooth. The pain of caries is due to the inflammatory reaction which results from infection of the pulp.

**Etiology.**—The etiological agents may be divided into predisposing causes and exciting causes. The predisposing causes may be further subdivided into constitutional factors, *e. g.*, diet and heredity, and local factors, *e. g.*, anatomical, local hygiene, and the condition of the saliva. There is general agreement that the *exciting cause* is bacterial infection with acid-producing organisms, which break up the carbohydrates of the food débris with liberation of organic acids. Bunting believes that caries is a specific entity caused by infection with *Lactobacillus acidophilus*, and many workers are of this opinion, while others think that non-hemolytic streptococci and other organisms may act in a similar manner. The digestion of the organic matrix of the dentine may be brought about by the *lactobacillus* or perhaps by putrefactive strains of bacteria.

It is with regard to the *predisposing factors* that the greatest difference of opinion exists. The experimental work of May Mellanby with vitamin D and Howe and Wolbach with vitamin A has shown that avitaminosis leads to defective formation of the developing teeth, but there is no general agreement that there is any necessary relation between this defective formation and the development of caries. It is hardly safe to say more than that diet, in some manner apparently not depending on deficiency of any one ingredient, plays some part in the production of caries. There can be no doubt that a well-balanced diet, especially one lacking in cereals which have an inhibitory influence on calcification of the teeth, is the best preventative of caries. In the little island of Tristan da Cunha, isolated in the south Atlantic, there is a community of white people with less caries than anywhere else in the world, and on this island no cereals can be grown owing to an infestation with rodents. It is of interest to note that there is not a single tooth brush on the island. A constitutional factor of undoubted importance is heredity. Some families are almost immune to caries, while in others every member shows the disease in advanced form.

*Local factors* are of equal or greater importance. Anatomical defects in the shape of occlusal fissures in the enamel give the bacteria the opportunity to work unmolested with no danger of the acids they produce being washed away by the saliva. Local hygiene plays a part. While it is not true that a clean tooth is necessarily a healthy one, it stands to reason that continued removal of food débris will tend to prevent the establishment of the conditions favorable to the development of caries. The saliva is a local factor which may be of great importance. In some mouths *lactobacilli* fail to flourish even when repeatedly introduced. This may depend on the pH of the saliva, or on other salivary factors so far undetermined. When caries begins on a smooth enamel surface it is due to the formation of a "bacterial plaque," a colony of bacteria which becomes attached to the surface

as the result of some property of the saliva. The acids formed under this plaque are prevented from diffusing, and act locally on the enamel. Thus immunity to caries may be due to faultless enamel, or to the fact that the environmental conditions are inimical to the growth of saprophytes in spite of the presence of deep fissures in the enamel. From the above brief review it is evident that we can agree with the statement that "the complete story of the causation of dental caries cannot yet be written" (Appleton).

### PERIAPICAL ABSCESS

We have already seen that when the integrity of the enamel is destroyed, infection readily passes along the dentinal tubules to reach the pulp. The result may vary from a mild pulpitis to severe suppuration, necrosis and gangrene of the pulp. The infection tends to extend through the apical foramen which admits the vessels and nerves, and may set up an acute periodontitis or a chronic apical periodontitis (dental granuloma). An acute periodontitis is likely to take the form of an abscess at the root of the tooth. This may remain circumscribed as a *root abscess* (Fig. 500) or the supuration may spread into the surrounding bone (osteomyelitis) with the formation of an *alveolar abscess*. Such an abscess tends to discharge into the mouth either on the lingual or the labial side of the alveolar process. When the abscess is in the mandible, it may discharge on the skin surface. The regional submaxillary lymph nodes are swollen and tender.

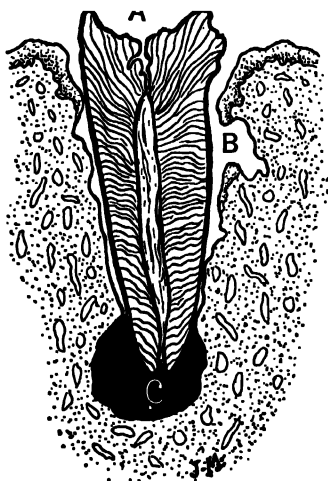


FIG. 500.—Dental disease. A, Caries affecting crown of tooth and penetrating down to the pulp. B, Pyorrhea: shrinking of bone and gum away from tooth. C, Root abscess.

A *dental granuloma* or chronic apical periodontitis is a condition characterized by the formation of a mass of chronic inflammatory tissue around the apex of a tooth. It therefore contains polymorphonuclear leucocytes, lymphocytes, plasma cells, mononuclear phagocytes, and fibroblasts in varying proportion, and is surrounded by a connective tissue capsule which blends with the healthy periodontal membrane, thus uniting the "growth" to the tooth. More distinctive is the presence of masses of squamous epithelium, probably derived from the "paradental epithelial debris" of Malassez. These are cell clusters found almost constantly in the periodontal membrane, and represent the remains of the enamel organ which extends as an epithelial sheath around the root (sheath of Hertwig) before the eruption of the tooth.

The epithelial masses may proliferate as the result of the chronic irritation, and finally undergo cystic degeneration to form dental or radicular cysts.

### PYORRHEA ALVEOLARIS

Like caries this condition is very common, but it is entirely unrelated to caries. Caries is a disease of the young; pyorrhea is more common after the age of thirty-five. In Tristan da Cunha, where caries is almost non-existent, pyorrhea is quite prevalent. Caries is a disease of the tooth; pyorrhea is a disease of the surroundings of the tooth. It is a chronic inflammatory process, commonly associated with suppuration, involving the alveolar process, the periodontium, and the gums, and results in loosening and loss of the teeth. For this reason there is a tendency to discard the term pyorrhea in favor of such names as periodontal infection, pericementitis, and paradentosis (the newest and perhaps the best).

The primary lesion is an atrophy of the alveolar margin and the periodontal membrane (pericementum), as a result of which a gingival crevice is formed by separation of the oral from the enamel epithelium. As long ago as 1771 that great student of disease, John Hunter, made the observation that marginal alveolar atrophy is the first lesion in pyorrhea. This crevice increases in depth and becomes lined by a downgrowth of oral epithelium. When the process of rarefaction and absorption extends sufficiently far, the tooth becomes loose and finally is lost. The condition is therefore in no sense a disease of the tooth. As soon as the tooth falls out or is extracted recovery occurs, but spontaneous recovery is impossible as long as the tooth remains in the jaw, for there is constant reinfection of the gingival space together with calcareous deposits on the root. The deep gingival crevice may be compared with the fissure on the occlusal surface of the tooth which forms the common starting point of caries. The food lodges in this crevice, infection occurs, and the result is a chronic suppuration of the periodontal membrane and the gum margins with accompanying discharge of pus. The gums are swollen, spongy, soft, and bleed easily; they may be dark red or pale. As the result of the suppuration the epithelium lining the crevice undergoes necrosis, and the bacteria invade the surrounding tissue. As a rule, however, the patient with pyorrhea appears to be in perfect health. The earliest *microscopic change* is a round-celled infiltration of the connective tissue at the apex of the gum margin. This infiltration spreads along the lymphatics under the epithelium lining the gingival trough and down the periodontal membrane. Fish is of the opinion that this chronic lymphangitis is responsible for the sequence of events, the chronic irritation causing the cementum to be absorbed and the epithelium to be stimulated to grow down and become attached to the healthy cementum.

The etiology of pyorrhea has been the cause of much dispute, and, as in the case of caries, the factors to be considered are both constitutional and local. It appears probable that *constitutional causes* play



a part in the alveolar atrophy which is the *fons et origo* of the condition. There is an osteoporosis and rarefaction which may be compared with that of osteitis fibrosa. Box describes a rarefying pericementitis fibrosa, which allows a falling away of the gums from the tooth and the creation of a pocket. As in osteitis fibrosa and Paget's disease of bone there appears to be a disturbance in the balance of bone apposition and resorption. Many cases show an increase in the blood calcium. The blood phosphate is often low. It appears probable from experimental work on animals that the most important predisposing cause is a fault of nutrition, possibly connected with avitaminosis and disturbance of the acid-base balance of the blood. There is no consensus of opinion as to whether any particular vitamin is at fault, but in the dog it has been found that vitamin A deficiency causes absorption of the alveolar process. The prevalence of pyorrhea in Tristan da Cunha may be related to the one-sided character of the diet. In support of the constitutional basis of the disease it may be noted that there is a close and frequent relationship between pyorrhea and diabetes mellitus.

The *local factors* take the form of local irritation and trauma, and may be regarded as exciting causes. The trauma caused by faulty occlusion of opposing teeth, loss of contact between the teeth, faulty fillings, and the formation of calcareous deposits, may, in the opinion of dental authorities, cause that recession of the bone from the tooth which is the essence of periodontal infection. The bacteriology is not constant. Non-hemolytic streptococci are most commonly found in the pus pockets and invade the gum. Spirochetes and fusiform bacilli are remarkably constant, but they are found in the presence of any decomposing organic material. *Entamoeba gingivalis* is frequently present, but appears to be quite non-pathogenic. Although infection is secondary and not primary, it is to the infection that any systemic results are due.

### FOCAL INFECTION

The general subject of focal infection has already been considered in Chapter VI, and the distinction drawn between focal infection and of focus of infection. A focus of infection is a circumscribed area infected with bacteria which have caused a local tissue reaction. With such a focus there are the following theoretical possibilities: (1) The bacteria may pass into the lymphatics and cause lymphadenitis of the regional lymph nodes. (2) They may enter the blood stream, multiply there, and set up an acute or chronic septicemia. (3) They may not multiply in the blood, but may settle in some distant part and multiply there. This is what is usually known as focal infection. (4) They may remain localized, but their toxins may be absorbed and set up degenerative and fibrotic changes in distant organs.

There are three possible foci of infection in relation to the teeth: (1) chronic periapical infection (root abscess, dental granuloma), (2) infection of the dental pulp, and (3) pyorrhea alveolaris. Of these, by

far the most important is the dental granuloma, because of its confined character which facilitates absorption of bacteria into the vessels.

The observations and conclusions of Fish and MacLean on the relation of oral streptococci to focal infection are remarkably interesting. They found that cultures from the roots of extracted teeth, irrespective of the condition of the tooth, always showed streptococci, although there was no microscopic evidence of inflammation in the periapical tissue. The conclusion they draw is that the germs gain entrance to the root during extraction. In chronic infection the streptococci are confined to a necrotic nidus surrounded by leucocytes or they may take refuge in the dental canals. Thus a position of stale-mate is established: the leucocytes are killed if they go in and the streptococci are killed if they venture out. The organisms do not live in the living dental and paradental tissues, but they irritate them with their toxins. Fish and MacLean made the remarkable observation that streptococci appear in the blood within five minutes of extracting teeth in pyorrhea, and even chewing hard candies has the same effect of pumping germs from the infected gums into the blood. The blood soon becomes sterile, sometimes in ten minutes.

Almost every conceivable lesion has at one time or another been attributed to foci of infection in connection with the teeth. The following list of diseases is less open to criticism than the lengthy lists often drawn up by the enthusiastic advocates of focal infection; chronic infective arthritis, myositis, endocarditis, nephritis, iritis and iridocyclitis. The problem is usually attacked from the angle of the patient suffering, say, from arthritis, and, as might be expected, roentgen-ray examinations will often reveal the presence of a quiet periapical granuloma. It is even more instructive to investigate the matter primarily from the dental standpoint. More than one large survey of university students with dental granulomas revealed by roentgen-rays has been made, and such a survey has always showed that the persons with dental foci of infection have no more arthritis or heart disease than do the normal controls.

### DIET AND THE TEETH

A large mass of experimental work has been carried out in recent years with the object of determining the relation between deficiencies of diet and defects in the developing teeth of animals. Many positive results have been recorded, but it is singularly difficult to apply these results to the problems of dental pathology in the human. Conditions in the mouths of such animals as the dog, the rat, and the guinea-pig differ widely from those which obtain in the human mouth. Moreover, different species vary widely in their reaction to dietary deficiency. Thus the rat is not affected by a deficiency of vitamin C (antiscorbutic), while the guinea-pig is unaffected by a deficiency of vitamin D (antirachitic), although the human child will develop scurvy and rickets as the result of such deficiency.

Wolbach and Howe believe that vitamin A deficiency is the most important of vitamin deficiencies in its effect on tooth formation. In their work on rats they found atrophy both of the enamel and the dentine in the developing incisor teeth. The initial effect is on the enamel organ, the enameloblasts atrophying first and then the rest of the organ. In the guinea-pig ossification of the enamel occurs in place of calcification. Atrophy of the odontoblasts follows, with defective formation of the dentine. Vitamin A appears to be responsible for the proper formation of the epithelium of the gum margin adjacent to the teeth, and if the vitamin is deficient this epithelium becomes hyperplastic and infected, with resulting gingivitis.

May Mellanby has worked extensively with vitamin D, and believes that deficiency of this vitamin holds the key to the problem of dental disease. She found that teeth of all textures could be produced in puppies by variations of the food in relation to vitamin D and calcium. A high calcium in the diet assists the vitamin, and helps to offset any vitamin deficiency. Cereals in large amount undoubtedly interfere with adequate calcification of the developing tooth. While it is true that the dentine is homologous to bone, it must be remembered that this is not equally true of the enamel which is an epithelial structure. Teeth are well formed in races where breast-feeding is prolonged, where there is a plentiful intake of vitamin D, and where sunlight has ready access to the exposed body.

Vitamin C seems to be necessary for healthy gums. Deficiency in this vitamin, as in scurvy, soon leads to sponginess, bleeding and infection of the soft tissues.

There is general agreement as to the fact that an adequate well-balanced diet is one of the most important factors in the formation of sound teeth and the prevention of caries, but it appears premature at present to ascribe a major rôle to any one constituent such as a particular vitamin. The ratio of calcium to phosphorus appears to be of importance, for rats tend to develop caries when there is a relative deficiency of phosphorus in the diet.

### MOTTLED ENAMEL

It is well known that infectious fevers in childhood may leave their mark on the enamel of the teeth, just as they may affect the structure of the nails. The term mottled enamel, however, is restricted to a peculiar condition which is markedly endemic in its distribution, affecting particularly the Mississippi Valley and the Rocky Mountain regions of North America, and certain well-defined districts in Europe. It may be prevalent in a community, only to disappear when the water supply is changed. The enamel of the teeth has an opaque white appearance, and may be stained yellow, brown, or even black. The surface may be corroded, owing to an absence of the cementing substance between the enamel rods, but there is no relation to caries. It is apparently due to an excess of fluorine in the water, the danger

line being 2 parts of fluorine per million. A similar condition can be produced in young rats by feeding with sodium fluoride. It develops in children during the first three or four years of life, a period at which the enamel is undergoing calcification. Change of the water supply or distillation of the water results in absolute prevention, but fails to restore the affected teeth to the normal.

**Hypoplasia.**—Hypoplasia of the enamel is caused by interference with the function of the enamel-forming tissue during development. This interference may be due to any serious disturbance of nutrition, but most often follows infectious diseases that affect the epithelium, *e. g.*, the acute exanthemata such as scarlet fever and measles. The defect takes the form of irregular pits upon the crowns of the teeth. In severe cases the crowns of all the teeth may be extensively honey-combed, the incisors being most frequently involved. The well-known lesions of the teeth in congenital syphilis (Hutchinson teeth) are examples of interference with the development of the enamel due to a systemic infection.

**Odontogenic Tumors.**—Tumors derived from dental or potential dental tissue may arise from the epithelial or the mesenchymal structures of the tooth. The epithelial tumor, the adamantinoma or enameloblastoma, arises from the enamel organ, and has already been considered on page 311. The mesenchymal tumors are odontogenic fibroma, dentinoma and cementinoma. Even more frequently the tumors are of mixed epithelial and mesenchymal structure. Excellent illustrations of the various forms will be found in the paper by Thoma and Goldman.

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